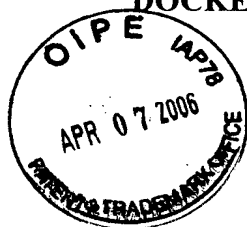


DOCKET NO.: AM100279 (WYNC-0677)

PATENT



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Adam M. Gilbert and Gary P. Stack

Confirmation No.: 3576

Application No.: 10/663,533

Group Art Unit: 1625

Filing Date: September 16, 2003

Examiner: Evelyn Mei Huang

For: 8-AZA-BICYCLO[3.2.1]OCTAN-3-OL DERIVATIVE OF 2,3-DIHYDRO-1,4-BENZODIOXAN AS 5-HT_{1A} ANTAGONISTS

EXPRESS MAIL LABEL NO: EV 765639635 US

DATE OF DEPOSIT: April 7, 2006

EV765639635US

MS Appeal Brief - Patent
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**APPEAL BRIEF TRANSMITTAL
PURSUANT TO 37 CFR § 1.192**

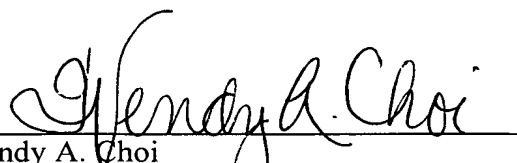
Transmitted herewith is the AMENDED APPEAL BRIEF in this application with respect to the Notification of Non-Compliant Appeal Brief received by The United States Patent and Trademark Office on **March 9, 2006**.

- ☐ Applicant(s) has previously claimed small entity status under 37 CFR § 1.27 .
- ☐ Applicant(s) by its/their undersigned attorney, claims small entity status under 37 CFR § 1.27 as:
- ☐ an Independent Inventor
 - ☐ a Small Business Concern
 - ☐ a Nonprofit Organization.
- ☐ Petition is hereby made under 37 CFR § 1.136(a) (fees: 37 CFR § 1.17(a)(1)-(4) to extend the time for response to the Office Action of _____ to and through comprising an extension of the shortened statutory period of _____ month(s).

	SMALL ENTITY		NOT SMALL ENTITY	
	RATE	FEE	RATE	FEE
<input type="checkbox"/> APPEAL BRIEF FEE	\$250	\$	\$500	\$0
<input type="checkbox"/> ONE MONTH EXTENSION OF TIME	\$60	\$	\$120	\$0
<input type="checkbox"/> TWO MONTH EXTENSION OF TIME	\$225	\$	\$450	\$0
<input type="checkbox"/> THREE MONTH EXTENSION OF TIME	\$510	\$	\$1020	\$0
<input type="checkbox"/> FOUR MONTH EXTENSION OF TIME	\$795	\$	\$1590	\$0
<input type="checkbox"/> FIVE MONTH EXTENSION OF TIME	\$1080	\$	\$2160	\$0
<input type="checkbox"/> LESS ANY EXTENSION FEE ALREADY PAID	minus	(\$)	minus	(\$0)
TOTAL FEE DUE		\$0		0

- ☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to Deposit Account 23-3050. This sheet is provided in duplicate.
- ☐ A check in the amount of \$.00 is attached. Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.
- ☐ Please charge Deposit Account No. 23-3050 in the amount of \$.00 . This sheet is attached in duplicate.
- ☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment of the fees associated with this communication to Deposit Account No. 23-3050.

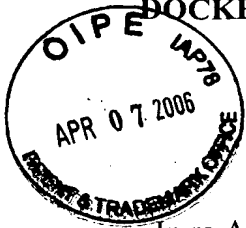
Date: April 7, 2006


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04-10-06

AF
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DOCKET NO.: AM100279 (WYNC-0677)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Adam M. Gilbert
and Gary P. Stack**

Confirmation No.: **3576**

Serial No.: **10/663,533**

Group Art Unit: **1625**

Filing Date: **September 16, 2003**

Examiner: **Huang, Evelyn Mei**

For: **8-AZA-BICYCLO[3.2.1]OCTAN-3-OL DERIVATIVES OF 2,3-DIHYDRO-
1,4-BENZODIOXAN AS 5-HT_{1A} ANTAGONISTS**

EXPRESS MAIL LABEL NO: EV 765639635 US
DATE OF DEPOSIT: April 7, 2006

Mail Stop Appeal Brief Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. § 1.192

This *amended* Appeal Brief is being filed in response to the December 13, 2005, Order of the Board of Patent Appeals and Interferences requiring Appellant to submit a missing Evidence Appendix and a missing Related Proceedings Appendix, as set forth in 37 CFR § 41.37(c)(1)(ix) and (c)(1)(x), respectively. The original Appeal Brief was timely filed April 11, 2005 in support of Appellant's appeal from the rejections of claims 26 and 33 to 52 dated September 21, 2004. A Reply Brief to the Examiner's Answer was timely filed on September 12, 2005. Aside from the new heading for the Evidence and Related Proceedings Appendices and non-substantive formatting changes, no new material has been added.

1. REAL PARTY IN INTEREST

Based on information supplied by Appellant and to the best of the undersigned's knowledge, the real party in interest in the above-identified patent application is Wyeth.

2. RELATED APPEALS AND INTERFERENCES

No related appeals or interferences are pending. See appendix entitled RELATED PROCEEDINGS APPENDIX.

3. STATUS OF CLAIMS

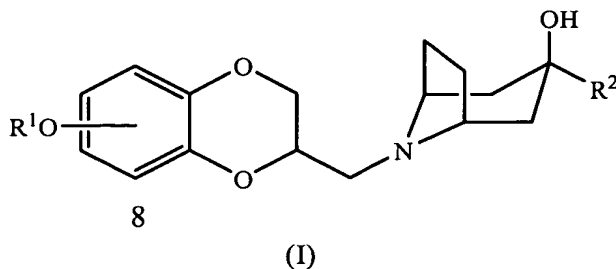
Claims 1 to 25 and 27 to 32 are cancelled. Claim 26 and 33 to 52 are pending and rejected. There are no claims that are allowed, withdrawn, or objected to. See appendix entitled CLAIMS APPENDIX.

4. STATUS OF AMENDMENTS

The Amendment after Final Rejection, filed December 20, 2004, was entered.

5. SUMMARY OF CLAIMED SUBJECT MATTER

Claims 26 and 33 to 52, as set forth in the CLAIMS APPENDIX, are directed to a method of treating a subject suffering from a condition selected from Alzheimer's disease, appetite control, disorders of thermoregulation, and sleep dysfunction, comprising the step of providing to said subject a therapeutically effective amount of a compound of formula I:



(page 1, line 26 to page 3, line 10).

The compounds of formula I are 5-HT_{1A} serotonin receptor antagonists. The appellants have demonstrated that the compounds of formula I have 5-HT_{1A} serotonin

- 3 -

receptor antagonist activity through two art recognized assays (page 9, line 1 to page 10, line 23). The first assay is the 3H-paroxetine binding assay, which assesses affinity of drugs for the serotonin transporter. The second assay assesses the agonism/antagonism at the 5HT_{1A} receptor using [³⁵S]-GTPγS binding to cloned human 5-HT_{1A} receptors. Appellants have also provided data to show that representative compounds of formula I have potent affinity for and antagonist activity at brain 5-HT_{1A} serotonin receptors (page 11, lines 1 to 8).

As 5-HT_{1A} serotonin receptor antagonists, the compounds of formula I are expected to be useful in the treatment of Alzheimer's disease and physiological phenomena that are at least in part under serotonergic influence, including appetite, thermoregulation, and sleep (page 11, lines 15 to 17).

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 26 and 33 to 52 are rejected as allegedly nonenabled under 35 U.S.C. § 112, first paragraph.

7. ARGUMENT

It is has not been prima facie established that claims 26 and 33 to 52 are not enabled under 35 U.S.C. § 112, first paragraph

In order to establish a *prima facie* case of non-enablement, the following must be established by the Patent Office:

1. a rational basis as to
 - a. why the disclosure does not teach; or
 - b. why to doubt the objective truth of the statements in the disclosure that purport to teach;
2. the manner and process of making and using the invention
3. that correspond in scope to the claimed invention
4. to one of ordinary skill in the pertinent technology,
5. without undue experimentation, and

- 4 -

6. dealing with subject matter that would not already be known to the skilled person as of the filing date of the application.

Any rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement, must include evidence supporting each of these elements. Applicant respectfully submits that the Office has failed to meet its burden of establishing a *prima facie* case of non-enablement.

It has been consistently held that the first paragraph of 35 U.S.C. § 112 requires nothing more than *objective* enablement. Furthermore, a specification that teaches how to make and use the invention in terms which correspond in scope to the claims *must* be taken as complying with the first paragraph of 35 U.S.C. § 112, *unless* there is reason to doubt the objective truth of the statements relied upon therein for enabling support. *Stahelin v. Secher*, 24 U.S.P.Q.2d 1513, 1516 (B.P.A.I. 1992) (citing *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (C.C.P.A. 1971). “[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to ... back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.” *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971).

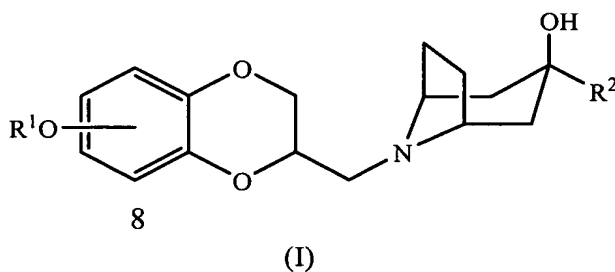
In the instant application, the Office alleges that there is no established nexus between antagonist activity at brain 5-HT_{1A} serotonin receptors and the treatment of Alzheimer's disease, appetite control, disorders of thermoregulation, and sleep dysfunction, as established in the literature or by data in the appellants' specification. In response to the rejection, appellants provided a number of scientific journal references that establish the nexus for each of the claimed conditions. The Office has taken the position that the references do not establish the nexus for appetite control, disorder of thermoregulation, and sleep dysfunction because each encompass opposite conditions. Accordingly, appellants have appealed the rejection because they believe that claims 26 and 33 to 52 are enabled under 35 U.S.C. § 112, first paragraph, and that, contrary to the Office's position:

- there is an established nexus between the antagonism at the 5-HT_{1A} receptor and treatment of the claimed conditions;
- it is not illogical or inconsistent for the compounds of formula I to be useful in methods of treating conditions that encompass seemingly opposite characteristics; and

- representative examples have been presented to establish that the compounds of formula I are 5-HT_{1A} receptor antagonists, commensurate with the scope of the claimed genus and sufficient for the degree of predictability in the art.

Established Nexus between 5-HT_{1A} Receptor Antagonists and Treatment of Alzheimer's Disease, Appetite Control, Disorders of Thermoregulation, and Sleep Dysfunction

Claims 26 and 33 to 52 are directed a method of treating a subject suffering from a condition selected from Alzheimer's disease, appetite control, disorders of thermoregulation, and sleep dysfunction, comprising the step of providing to said subject a therapeutically effective amount of a compound of formula I:



Appellants have provided the following references to establish the nexus between each of the listed conditions and the antagonism at the 5-HT_{1A} receptor:

<i>Condition</i>	<i>Reference showing nexus 5-HT_{1A} antagonist and condition</i>
Alzheimer's disease	Lanfume, <i>et al.</i> , <i>Current Drug Targets – CNS & Neurological Disorders</i> (2004) 3:1-10 (See page 5 in particular) Kwon, <i>et al.</i> , <i>Neurodegenerative Dis.</i> (2004) 1:113-52 (See page 145 and 147)
Appetite control	Moreau, <i>et al.</i> , <i>Brain Res. Bull.</i> (1992) 29(6): 901-4
Disorders of thermoregulation	Ootsuka, <i>et al.</i> , <i>J. Physiol.</i> (2003) 552(1): 303-14
Sleep dysfunction	Sorensen, <i>et al.</i> , <i>Behav. Brain Res.</i> (2001) 121(1-2): 181-7

Each of these references is included in the EVIDENCE APPENDIX.

Furthermore, there are also other literature references (full paper or abstract included in EVIDENCE APPENDIX) that show that treatment with compounds that affect 5HT_{1A} receptor functionality may be used to treat Alzheimer's disease, appetite control, disorders of thermoregulation, and sleep dysfunction:

Alzheimer's Disease

Schechter, L. E., *et al.*, *Curr. Pharm. Des.* (2002) 8(2),139-45 indicates that 5HT_{1A} receptor antagonists are being developed to provide treatment for Alzheimer's disease.

Appetite Control

Ebenezer *et al.*, *Physiol Behav.* (1999) 67(2), 213-7 and Ebenezer *et al.*, *Physiol. Behav.* (2001) 73(1-2), 223-7 describe the use of the 5HT_{1A} receptor agonist 8-OH-DPAT to decrease operant food intake by food-deprived pigs and increase feeding behavior in satiated pigs, suggesting that 5HT_{1A} receptor antagonism could increase operant food intake in food-deprived subjects who nonetheless feel satiated, such as those suffering from anorexia.

Disorders of Thermoregulation

Brubacher, *et al.*, *Vet. Hum. Toxicol.*, (1996) 38(5), 358-61 confirms that excessive stimulation of 5HT_{1A} receptors causes a syndrome of serotonin excess that consists of, *inter alia*, hyperthermia.

Oerther, S., *Neuroreport.* (2000) 11(18):3949-51 demonstrates that the 5HT_{1A} receptor agonists 7-OH-DPAT and OH-DPAT produce hypothermia.

Sleep Dysfunction

Bjorvatn B. and Ursin R., *Rev. Neurosci.* (1998) 9(4), 265-73 demonstrates that systemic administration of 5HT_{1A} agonists consistently increases wakefulness and reduces slow wave sleep and REM sleep in humans.

Gillin J. C., *et al.*, *Psychopharmacology (Berl)* (1994) 116(4), 433-6 provides results indicating that systemic stimulation of 5HT_{1A} receptors prolong REM latency and inhibit REM sleep.

In sum, appellants submit that there is an established nexus between antagonism at the 5HT_{1A} receptor and the treatment of Alzheimer's disease, appetite control, disorders of sleep regulation, and sleep dysfunction.

Not Illogical to Treat Conditions that Encompass Seemingly Opposite Characteristics with Same Compounds

The Office asserts that it is not logical to use the same compound to treat seemingly opposite conditions. Appellants submit that the Office presents an oversimplified view of the etiological bases for serotonin-related disorders, including as hyperphagia/hypophagia, hyperthermia/hypothermia, insomnia/narcolepsy, and other seemingly "opposing and conflicting conditions." Appellants have explained above how the literature recognizes that Alzheimer's disease, appetite control, disorders of thermoregulation, and sleep disorders are, at least in part, under serotonergic influence. It is widely recognized that a therapy may serve to restore or ensure homeostasis with respect to a given physiological system (such as the cycle of serotonin production and uptake), which can in turn remedy disorders that derive from an excess or a deficiency of a fundamental component of the system (here, serotonin). For example, wakefulness, slow wave sleep, and REM sleep are all of central importance to all varieties of sleep dysfunction, including insomnia and narcolepsy (*e.g.*, the failure to attain the REM sleep state are features of both insomnia and narcolepsy), indicating that it is not "contradictory" to assert that mediation of 5HT_{1A} receptor activity would be useful in treating both of these disorders.

Accordingly, restoring stable 5HT_{1A} receptor functionality through administration of the compounds of formula I would constitute effective treatment for individuals suffering from these disorders.

Representative Examples Establish Compounds of Formula I are 5-HT_{1A} Receptor Antagonists

Contrary to the Office's assertion that a high degree of unpredictability exists in the 5HT_{1A} antagonist art (Advisory Action, page 2), appellants submit that they have presented

- 8 -

representative examples that establish that the compounds of formula I are 5-HT_{1A} receptor antagonists, commensurate with the scope of the claimed genus and sufficient for the degree of predictability in the art. Appellants further submit that the Office's position ignores the objectively reliable character of *in vitro* assays presented in specification.

The appellants have demonstrated that representative compounds of formula I have 5-HT_{1A} serotonin receptor antagonist activity through two art recognized assays (page 9, line 1 to page 10, line 23). The first assay is the 3H-paroxetine binding assay, which assesses affinity of drugs for the serotonin transporter. The second assay assesses the agonism/antagonism at the 5HT_{1A} receptor using [³⁵S]-GTPγS binding to cloned human 5-HT_{1A} receptors. Appellants have also provided data to show that representative compounds of formula I have potent affinity for and antagonist activity at brain 5-HT_{1A} serotonin receptors (page 11, lines 1 to 8).

Appellants submit that the skilled artisan would accept the disclosed model as reasonably correlating to the claimed effects and, as such, the Office must consider accept the object truth of the information unless there is evidence in the record to the contrary. *See In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995) (reversing the decision that *in vitro* data did not support *in vivo* applications); Manual of Patent Examining Procedure § 2164.02.

It is not the absence or presence of a structural relationship between known modulators of 5HT_{1A} receptor activity and the compounds of the present invention that induces appellants to extrapolate the results of the known modulators of 5HT_{1A} receptor activity as forms of treatment for various medical conditions to the inventive compounds, but rather the *functional* relationship, *viz.*, activity at the 5HT_{1A} receptor as demonstrated through reliable testing for ³H-paroxetine binding and 5HT_{1A} receptor antagonism, that permits appellants to provide compounds that utilize the nexus between the modulation of 5HT_{1A} receptor activity and the treatment of certain 5HT_{1A} receptor-effected medical conditions.

- 9 -

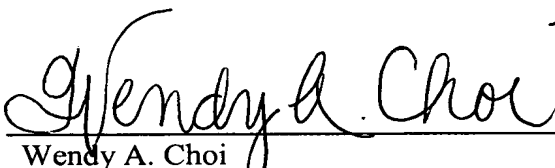
Accordingly, appellants submit that they have presented representative examples that establish that the compounds of formula I are 5-HT_{1A} receptor antagonists, commensurate with the scope of the claimed genus and sufficient for the degree of predictability in the art.

Conclusion

For the foregoing reasons, it is respectfully submitted that the Office has not met its burden of establishing that claims 26 and 33-52 are not enabled under 35 U.S.C. § 112, first paragraph. Appellants, therefore, request that this patent application be remanded to the Patent Office with an instruction to both withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph, and allow the appealed claims.

Respectfully submitted,

Date: *April 7, 2006*


Wendy A. Choi
Registration No. 36,697

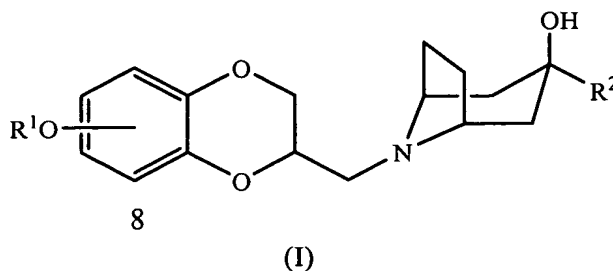
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CLAIMS APPENDIX

The following claims are involved in the present appeal:

26. A method of treating a subject suffering from a condition selected from the group consisting of Alzheimer's disease, appetite control, disorders of thermoregulation, and sleep dysfunction, comprising the step of:

providing to the subject suffering from said condition, a therapeutically effective amount of a compound of formula I



wherein

R^1 is a straight-chained alkyl of 1 to 6 carbon atoms, or a branched chain alkyl of 3 to 8 carbon atoms; and

R^2 is phenyl, naphthyl, anthracyl, phenanthryl, pyridyl, pyrimidyl, triazinyl, furyl, pyrrolyl, pyrazolyl, indolyl, imidazolyl, benzofuryl, benzothieryl, oxazolyl, or thiazolyl each optionally substituted with 0 to 3 substituents selected from straight-chain alkyl of 1 to 6 carbon atoms, branched-chain alkyl of 3 to 8 carbon atoms, alkoxy of 1 to 6 carbon atoms, mono- or dialkylamino of 1 to 6 carbon atoms, nitro, halo, amino, cyano, trifluoromethyl, trifluoromethoxy and hydroxy;

or a pharmaceutically acceptable salt thereof.

33. A method according to claim 26, wherein said subject is a human.
34. A method according to claim 26, wherein R^1 is a straight-chained alkyl of 1 to 3 carbon atoms, or a branched chain alkyl of 3 to 6 carbon atoms.

- 11 -

35. A method according to claim 26, wherein R^1 is a straight-chained alkyl of 1 or 2 carbon atoms.
36. A method according to claim 26, wherein R^2 is phenyl, naphthyl, pyridyl, pyrimidyl, furyl, pyrrolyl, pyrazolyl, indolyl, imidazolyl, benzofuryl, or benzothienyl; each optionally substituted with 1 to 3 substituents the same or different selected from straight-chain alkyl of 1 to 3 carbon atoms, branched-chain alkyl of 3 to 6 carbon atoms, alkoxy of 1 to 3 carbon atoms, mono- or di-alkylamino in which each alkyl group has 1 to 3 carbon atoms, nitro, amino, cyano, halogen, trifluoromethyl, trifluoromethoxy, and hydroxy.
37. A method according to claim 26, wherein R^2 is phenyl, naphthyl, pyridyl, pyrrolyl, indolyl, or benzothienyl; each optionally substituted with 1 to 3 substituents the same or different selected from nitro, amino, cyano, halogen, trifluoromethyl, trifluoromethoxy, and hydroxy.
38. A method according to claim 26, wherein R^2 is trifluoromethylphenyl or methoxyphenyl.
39. A method according to claim 26, wherein the R^1O substituent is bonded to the 1,4-benzodioxan nucleus at the 8 position.
40. A method according to claim 26, wherein R^1 is a straight-chained alkyl of 1 to 3 carbon atoms, or a branched chain alkyl of 3 to 6 carbon atoms and R^2 is phenyl, naphthyl, pyridyl, pyrimidyl, furyl, pyrrolyl, pyrazolyl, indolyl, imidazolyl, benzofuryl, or benzothienyl; each optionally substituted with 0 to 3 substituents selected from straight-chain alkyl of 1 to 3 carbon atoms, branched-chain alkyl of 3 to 6 carbon atoms, alkoxy of 1 to 3 carbon atoms, mono- or di-alkylamino in which each alkyl group has 1 to 3 carbon atoms, halogen, trifluoromethyl, trifluoromethoxy, and hydroxy.

41. A method according to claim 26, wherein R¹ is a straight-chained alkyl of 1 or 2 carbon atoms, and R² is phenyl, naphthyl, pyridyl, pyrrolyl, indolyl, or benzothienyl; each optionally substituted with a 0 to 3 substituents selected from nitro, amino, cyano, halogen, trifluoromethyl, trifluoromethoxy, and hydroxy.
42. A method according to claim 26, wherein R¹ is a straight chain alkyl of 1 or 2 carbon atoms and R² is trifluoromethylphenyl or methoxyphenyl.
43. A method according to claim 26, wherein said compound is (*S*)-8-(8-ethoxy-2,3-dihydrobenzo-[1,4]dioxin-2-ylmethyl)-3-naphthalen-2-yl-8-aza-bicyclo[3.2.1] octan-3-ol or a pharmaceutically acceptable salt thereof.
43. A method according to claim 26, wherein said compound is (*S*)-8-(8-ethoxy-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-3-phenyl-8-aza-bicyclo[3.2.1]octan-3-ol or a pharmaceutically acceptable salt thereof.
44. A method according to claim 26, wherein said compound is (*S*)-3-benzo[b]thiophen-3-yl-8-(8-ethoxy-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-8-aza-bicyclo[3.2.1] octan-3-ol or a pharmaceutically acceptable salt thereof.
45. A method according to claim 26, wherein said compound is 8-{[(2*S*)-8-ethoxy-2,3-dihydrobenzo-[1,4]dioxin-2-yl]methyl}-3-pyridin-2-yl-8-aza-bicyclo [3.2.1]octan-3-ol or a pharmaceutically acceptable salt thereof.
46. A method according to claim 26, wherein said compound is 8-{[(2*S*)-8-ethoxy-2,3-dihydrobenzo-[1,4]dioxin-2-yl]methyl}-3-(3-trifluoromethyl-phenyl)-8-aza-bicyclo[3.2.1]octan-3-ol or a pharmaceutically acceptable salt thereof.

- 13 -

47. A method according to claim 26, wherein said compound is 8-{[(2S)-8-methoxy-2,3-dihydro-1,4-benzodioxin-2-yl]methyl}-3-(2-methoxyphenyl)-8-azabicyclo[3.2.1]octan-3-ol or a pharmaceutically acceptable salt thereof.
48. A method according to claim 26, wherein said compound is 8-{[(2S)-8-methoxy-2,3-dihydro-1,4-benzodioxin-2-yl]methyl}-3-[3-(trifluoromethyl)phenyl]-8-azabicyclo[3.2.1]octan-3-ol or a pharmaceutically acceptable salt thereof.
49. A method according to claim 26, wherein said compound is 8-{[(2S)-8-methoxy-2,3-dihydro-1,4-benzodioxin-2-yl]methyl}-3-(2-pyridinyl)-8-azabicyclo[3.2.1]octan-3-ol or a pharmaceutically acceptable salt thereof.
50. A method according to claim 26, wherein said compound is 3-(1-benzothien-3-yl)-8-{[(2S)-8-methoxy-2,3-dihydro-1,4-benzodioxin-2-yl]methyl}-8-azabicyclo[3.2.1]octan-3-ol or a pharmaceutically acceptable salt thereof.
51. A method according to claim 26, wherein said compound is 8-{[(2S)-8-methoxy-2,3-dihydro-1,4-benzodioxin-2-yl]methyl}-3-phenyl-8-azabicyclo[3.2.1]octan-3-ol or a pharmaceutically acceptable salt thereof.
52. A method according to claim 26, wherein said compound is 3-((2S)-8-methoxy-2,3-dihydrobenzo-[1,4]dioxin-2-ylmethyl)-8-naphthalen-2-yl-3-aza-bicyclo[3.2.1]octan-8-ol or a pharmaceutically acceptable salt thereof.

EVIDENCE APPENDIX

The references referred to in the table below are enclosed.

Condition	Reference showing nexus 5-HT_{1A} antagonist and condition
Alzheimer's disease	<p>Lanfume, <i>et al.</i>, <i>Current Drug Targets – CNS & Neurological Disorders</i> (2004) 3:1-10 (See page 5 in particular)</p> <p>Kwon, <i>et al.</i>, <i>Neurodegenerative Dis.</i> (2004) 1:113-52 (See page 145 and 147)</p> <p>Schechter, L. E., <i>et al.</i>, <i>Curr. Pharm. Des.</i> (2002) 8(2),139-45</p>
Appetite control	<p>Moreau, <i>et al.</i>, <i>Brain Res. Bull.</i> (1992) 29(6): 901-4</p> <p>Ebenezer <i>et al.</i>, <i>Physiol Behav.</i> (1999) 67(2), 213-7</p> <p>Ebenezer <i>et al.</i>, <i>Physiol. Behav.</i> (2001) 73(1-2), 223-7 d</p>
Disorders of thermoregulation	<p>Ootsuka, <i>et al.</i>, <i>J. Physiol.</i> (2003) 552(1): 303-14</p> <p>Brubacher, <i>et al.</i>, <i>Vet. Hum. Toxicol.</i>, (1996) 38(5), 358-61</p> <p>Oerther, S., <i>Neuroreport.</i> (2000) 11(18):3949-51</p>
Sleep dysfunction	<p>Sorensen, <i>et al.</i>, <i>Behav. Brain Res.</i> (2001) 121(1-2): 181-7</p> <p>Bjorvatn B. and Ursin R., <i>Rev. Neurosci.</i> (1998) 9(4), 265-73</p> <p>Gillin J. C., <i>et al.</i>, <i>Psychopharmacology (Berl)</i> (1994) 116(4), 433-6</p>

DOCKET NO.: AM100279 (WYNC-0677)

PATENT

- 15 -

RELATED PROCEEDINGS APPENDIX

No related appeals or interferences are pending. Therefore, appellants are not providing copies of any related proceedings.

5-HT₁ Receptors

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Abstract: Among the seven classes of serotonin (5-hydroxytryptamine, 5-HT) receptors which have been identified to date, the 5-HT₁ class is comprised of five receptor types, with the 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} characterized by a high affinity for 5-carboxamido-tryptamine, the 5-HT_{1E} and 5-HT_{1F} characterized by a low affinity for this synthetic agonist, and all five having a nanomolar affinity for the endogenous indolamine ligand. The genes encoding 5-HT₁ receptors have been cloned in both human and rodents, allowing the demonstration that they all belong to the G-protein-coupled-receptor superfamily with the characteristic 7 hydrophobic (transmembrane) domain-containing amino acid sequence. All the 5-HT₁ receptor types actually interact with G_{ai}/G_{ao} proteins to inhibit adenylyl cyclase and modulate ionic effectors, i.e. potassium and/or calcium channels. Probes derived from the knowledge of amino acid sequence of the receptor proteins and of nucleotide sequence of their encoding mRNAs allowed the mapping of all the 5-HT₁ receptor types in the central nervous system and other tissues. For the last twenty years, both pharmacological investigations with selective agonists and antagonists and phenotypical characterization of knock-out mice have been especially informative regarding the physiological implications of 5-HT₁ receptor types. This research ends notably with the development of triptans, whose agonist activity at 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} receptors underlies their remarkable efficacy as antimigraine drugs. Clear-cut evidence of the implication of 5-HT₁ receptors in anxiety- and depression-like behaviours and cognitive performances in rodents should hopefully promote research toward development of novel drugs with therapeutic potential in psychopathological and dementia-related diseases.

1 - HISTORICAL SUMMARY / OVERVIEW

Since the introduction of radioligand binding techniques in the 1970's and the application of molecular cloning approaches from the late 1980's, the number of membrane-bound sites at which 5-hydroxytryptamine (5-HT, serotonin) is now known to act has proliferated. The demonstration of the existence of multiple classes of 5-HT receptors explains, at least in part, why and how this biogenic amine causes numerous physiological and pharmacological effects in various organs and tissues.

5-HT receptors were originally classified into two major subtypes, M and D, by Gaddum and Picarelli in 1957, based on their findings that 5-HT contracts the guinea-pig ileum through two different mechanisms: directly, by an effect on receptors located on smooth muscles (D receptors), and, indirectly, by an effect on neuronal receptors (M receptors) [1]. However, the start of the modern era of serotonin receptor research really began in 1979 with the advent of radioligand binding techniques when it was reported that 5-HT receptors could be divided into two classes based on their different affinities for serotonergic receptor agonists and antagonists: 5-HT₁ for those receptors displaying high affinity (nanomolar range) for serotonin and 5-HT₂ for those with low affinity (micromolar range) for serotonin but high affinity for some serotonin receptor antagonists [2]. As more specific 5-HT receptor agonists, antagonists and radioligands became available and recombinant DNA technology was

applied, it rapidly became apparent that this classification was a major oversimplification. It is now thought that the effects of 5-HT are mediated by 6 distinct classes of G protein-coupled receptor populations, namely: 5-HT₁, 5-HT₂, 5-HT₄, 5-HT₅, 5-HT₆ and 5-HT₇, and a family of ligand-gated ion channels with the appellation, 5-HT₃ [3, 4].

Many of these major groups are themselves comprised of several subtypes. This is notably the case of the 5-HT₁ family which was initially subdivided into 6 receptor subtypes named 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F}. However, the number was later restricted to five after the characterization of the cDNA encoding the 5-HT_{1C} receptor revealed its close homology with 5-HT₂ receptors (69 % vs. 29 % for 5-HT_{1A}) and it was found to have similar coupling to the phosphatidyl inositol second messenger system. 5-HT_{1C} has therefore been unambiguously renamed the 5-HT_{2C} receptor [3].

5-HT₁ receptors form the largest class of 5-HT receptor subtypes, first grouped together because of their high affinity for 5-HT [5]. In addition, with the exception of the 5-HT_{1E} and 5-HT_{1F} subtypes, all the receptors in this class exhibit a high affinity for the synthetic agonist, 5-carboxamido-tryptamine (5-CT), while all 5 members share coupling with G_{ai}/G_{ao} proteins to inhibit adenylyl cyclase (AC) and/or modulate other signaling pathways and ionic effectors (see below). Furthermore, their 40-60% overall sequence homology [6] justifies membership to the same receptor class and this nomenclature has become part of the IUPHAR accepted classification of 5-HT receptors.

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2 - 5-HT_{1A} RECEPTORS

The 5-HT₁ receptor was initially thought to comprise two recognition sites, designated 5-HT_{1A} and 5-HT_{1B} on the basis of high and low affinity displacement of [³H] 5-HT by spiperone [7]. Using 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin), which was, at the time thought of as a very atypical 5-HT receptor agonist, Middlemiss and Fozard found that this compound had high affinity and selectivity for the 5-HT_{1A} recognition site [8]. Simultaneously, Gozlan *et al.* had identified a specific binding site in rat brain membranes for [³H] 8-OH-DPAT [9]. Numerous *in vitro* and *in vivo* studies of 8-OH-DPAT and other 5-HT receptor agonists and antagonists suggested that 5-HT_{1A} was more than an inflection on a radioligand binding isotherm [10] but full acceptance that the 5-HT_{1A} recognition site was indeed a functional receptor was achieved by application of recombinant DNA technology.

2 - 1 - Cloning

The genomic clone encoding the human 5-HT_{1A} receptor was the first 5-HT receptor clone to be isolated in 1987 [11]. However, it was formally identified as the nucleotide sequence coding for the pharmacologically defined 5-HT_{1A} receptor only the following year [12]. Briefly, a DNA fragment in the human genome was initially cloned and sequenced after it was found to cross-hybridize with a full-length β_2 adrenergic receptor cDNA at low stringency [11]. This genomic clone, designated "G-21", was found to contain an intronless gene located on human chromosome 5 (q11.2-q13) that encodes a predicted protein of 422 amino acids. A first series of radioligand binding studies failed to

detect any specific binding of ligands for β_1 - α_1 - and α_2 -adrenergic receptors, as well as for dopamine D₁ and D₂ receptors on cells transfected with the G-21 encoding sequence [11]. However, subsequent studies revealed specific binding of [¹²⁵I]-iodocyanopindolol, a radioligand that labels not only β -adrenergic receptors, but also 5-HT_{1A} and 5-HT_{1B} serotonergic receptors [12]. The actual existence of the 5-HT_{1A} receptor was further confirmed by the specific binding of the selective 5-HT_{1A} agonist radioligand, [³H]8-OH-DPAT, in the rat brain [9].

The rat 5-HT_{1A} receptor was then cloned, expressed in transfected cells and fully characterized by Albert *et al.* in 1990 [13]. This receptor was shown to derive from an intronless open reading frame encoding a 422-amino acid protein with seven hydrophobic (putative transmembrane) domains (Fig. 1) that is 89% identical to the human 5-HT_{1A} receptor. Transfection of different eukaryotic cell lines with the encoding sequence led to expression of a binding site with a pharmacological profile typical of the 5-HT_{1A} receptor. The cloned rat 5-HT_{1A} receptor was shown to be coupled to inhibition of cAMP accumulation. Interestingly, mRNA encoding the 5-HT_{1A} receptor apparently exists as three different species (3.9, 3.6 and 3.3 kb) in the rat but as only one species in human. All these data for the rat 5-HT_{1A} receptor clone were independently confirmed by another group using a different rat genomic library [14, 15]. Later on, the mouse homologue was also cloned [16]. Thus, a 2.4 kb cDNA containing a single open reading frame that displayed high homology (> 85% identity in the predicted amino acid sequence) with the human and rat 5-HT_{1A} receptor genes was cloned from the 5-HT_{1A} receptor expressing SN-48 mouse cell line. When transfected into 5-

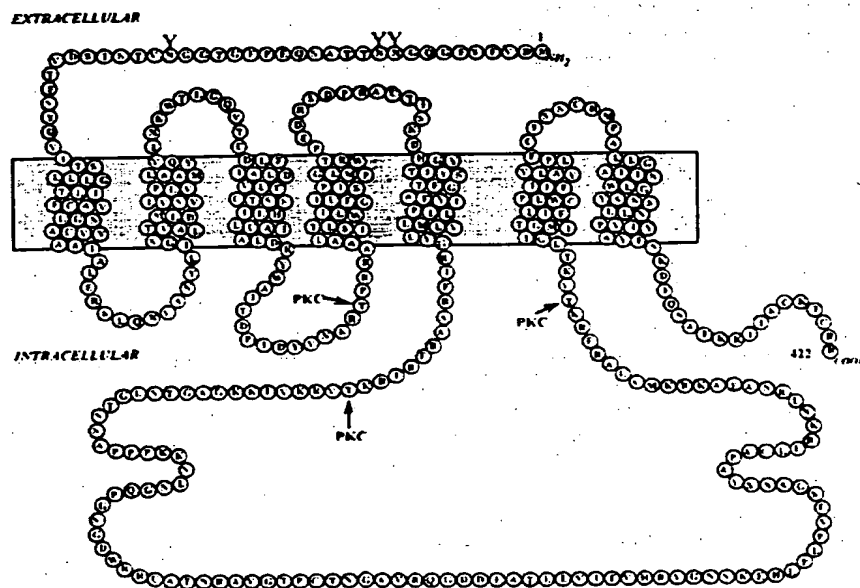


Fig. (1). Putative transmembrane organisation of the rat 5-HT_{1A} receptor (adapted from ref. 10).

The receptor has seven hydrophobic domains that probably correspond to membrane-spanning regions. Consensus sites for phosphorylation by protein kinase C (PKC) and N-glycosylation (Y) are indicated.

HT_{1A} receptor-negative Ltk- cells, this cDNA was also found to direct expression of the murine 5-HT_{1A} receptor [16].

2 - 2 - Distribution

Immunocytochemical and binding studies, as well as *in situ* hybridization histochemistry, revealed that the 5-HT_{1A} receptor is widely distributed in the rat brain, with a particularly high density in the limbic system.

Regional Distribution of 5-HT_{1A} Receptor mRNA

The regional distribution of the mRNA encoding the 5-HT_{1A} receptor was investigated in rat brain sections using *in situ* hybridization histochemistry with [³²P]labeled nucleoprobes, corresponding to highly selective portions within the third intracellular loop and the N terminus domain of the 5-HT_{1A} receptor amino acid sequence. These probes allowed the visualization of 5-HT_{1A} mRNA mainly in regions where 5-HT_{1A} receptor binding sites were previously found [17]. These data were the first to suggest that 5-HT_{1A} receptors are not transported distal to their site of synthesis and are very probably targeted into the somatodendritic compartment of neurons.

Subcellular Localization of 5-HT_{1A} Receptors

Rat specific 5-HT_{1A} receptor antibodies raised in a rabbit injected with a synthetic peptide corresponding to a highly selective portion of the third intracellular loop of the receptor protein were used for the immunohistochemical mapping of 5-HT_{1A} receptors in rat brain [18]. The highest density of immunostaining was found in limbic areas (lateral septum, CA1 area of Ammon's horn and dentate gyrus in the hippocampus, frontal and entorhinal cortices), anterior raphe nuclei, and the interpeduncular nucleus. In contrast, extrapyramidal areas, including the caudate putamen, the globus pallidus and the substantia nigra, as well as the cerebellum, exhibited very low to no immunostaining by anti-5-HT_{1A} receptor antibodies. In general, the distribution and density of 5-HT_{1A} receptor-like immunoreactivity in the whole brain and spinal cord were consistent with the mapping of 5-HT_{1A} receptor binding sites and 5-HT_{1A} receptor mRNA established by autoradiographic and *in situ* hybridization procedures [17, 19].

Furthermore, double immunohistochemical staining with anti-5-HT_{1A} receptor antibodies and anti-5-HT antibodies led to the conclusion that all the cells endowed with 5-HT_{1A} receptor immunoreactivity in the dorsal raphe nucleus and the vast majority of those in the median raphe nucleus are the serotonergic neurons [20]. However recent data suggested that a small but significant population of 5-HT-immunonegative cells could also express the 5-HT_{1A} receptor in the dorsal raphe nucleus [21].

Anti-5-HT_{1A} receptor antibodies also allowed the subcellular distributions of 5-HT_{1A} receptors to be investigated in the dorsal raphe nucleus and hippocampal formation using light and electron microscopic immunocytochemistry. In the dorsal raphe nucleus, 5-HT_{1A} receptor immunoreactivity was found exclusively on neuronal cell bodies and dendrites, especially along extrasynaptic portions of their plasma membrane. In the hippocampal formation, mainly dendrites of pyramidal and

granule cells displayed 5-HT_{1A} receptor immunoreactivity [19, 22]. In both regions, immunogold labeling clearly showed that 5-HT_{1A} receptor immunostaining is mainly confined to the plasma membrane, with only a small proportion of 5-HT_{1A}-like immunoreactivity in the cytoplasm of 5-HT cells in the dorsal raphe nucleus and pyramidal cells in the hippocampus of control, untreated, rats [23].

Regional Distribution of 5-HT_{1A} Receptors in Brain: Quantitative Autoradiographic Studies

The mapping of 5-HT_{1A} receptors in the rat brain was established as soon as the first selective radioligand, [³H]8-OH-DPAT, became available [9, 24]. Later on, several other radioligands were synthesized which generally proved to be as efficient as [³H]8-OH-DPAT for the labeling of these receptors in brain membranes and sections (see [25] for a review). The autoradiographic pictures obtained with these molecules fully confirmed the data obtained with the first selective radioligand [³H]8-OH-DPAT [26]. Among these radioligands, the tritiated derivative of the 5-HT_{1A} receptor antagonist [³H]N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl) cyclohexane carboxamide ([³H]WAY 100635) [27] is of special interest because it allows high affinity labeling of both G-protein-coupled and free 5-HT_{1A} receptor binding subunits in brain membranes (whereas [³H]8-OH-DPAT and other agonist radioligands allow high affinity labeling of G-protein coupled 5-HT_{1A} receptors only [9]).

All these studies showed that 5-HT_{1A} receptor binding sites are especially abundant in the gyrus dentatus and CA1 area of Ammon's horn in the hippocampus, the lateral septum, the entorhinal and frontal cortex, and the dorsal raphe nucleus. Significant but lower expression of 5-HT_{1A} receptors has also been reported in some thalamic and hypothalamic nuclei. In contrast, these receptors are hardly detected in the striatum (except in its postero-lateral portion), substantia nigra and cerebellum.

The selective lesion of the somas and dendrites of serotonergic neurons caused by the local microinjection of the neurotoxin 5,7-dihydroxytryptamine is associated with the disappearance of specific [³H]8-OH-DPAT binding sites in the dorsal raphe nucleus [28], in line with double immunohistochemical staining data (with anti-5-HT_{1A} receptor antibodies and an anti-serotonin antiserum) showing the expression of 5-HT_{1A} receptors by 5-HT neurons in this nucleus [20].

In human, recent studies using PET scan approaches confirmed the localization observed in rodents. In particular, [carbonyl-¹¹C]WAY-100635 [29] allowed the demonstration that 5-HT_{1A} receptors are especially abundant in limbic areas and the dorsal raphe nucleus. Other radioligands were subsequently developed, such as p-[¹⁸F]MPPF, a fluoro analog of WAY-100635 [30], and these probes are now regularly used for assessing possible changes in 5-HT_{1A} receptor expression in subjects suffering from various psychiatric or neurological diseases.

2 - 3 - Coupling

5-HT_{1A} receptors have been shown to be coupled to various effectors, such as ionic channels, adenylyl cyclase

and/or kinases via a G α i/G α o protein (see [6]). Convergent data obtained in numerous transfected cell lines demonstrated that 5-HT_{1A} receptors can bind to several G proteins, with affinity decreasing in the following order: G α i3>G α i2>G α i1>G α o>G α z. Indeed, coupling of the 5-HT_{1A} receptor to a given G protein may be influenced by the type of agonist acting at the receptor [31]. In addition, regional differences in G proteins coupled to 5-HT_{1A} receptors have been recently demonstrated using immunoaffinity chromatography with anti-5-HT_{1A} receptor antibodies followed by immunoblotting with specific anti-G α subunit antibodies [32]. These data, which demonstrated that 5-HT_{1A} receptors are mainly coupled to G α o in the hippocampus, to G α o and G α i3 in the frontal cortex, to G α i3 in the dorsal raphe nucleus, and to G α i1, G α i3 and G α z in the hypothalamus [32], were further confirmed by immunoprecipitating G proteins after their labeling in membranes incubated with both [³⁵S]GTP- γ -S and 5-HT_{1A} receptor agonists. Such variations in the type of G α -proteins coupled to 5-HT_{1A} receptors might explain the regional differences in adaptive regulation of these receptors which have been reported after chronic blockade of 5-HT reuptake or exposure to stressful conditions in rats [33, 34], and in 5-HT transporter knock-out mice [35]. Furthermore, they could explain the partial versus full agonist properties of several ligands depending on the *in vitro* or *in vivo* assays used to assess their efficacy at 5-HT_{1A} receptors (see [36]).

It is well established that 5-HT_{1A} receptor stimulation triggers the opening of G protein-gated inwardly rectifying potassium (GIRK) channels in hippocampal and dorsal raphe neurons as well as in rat atrial myocytes in primary cultures [37 - 41]. However, to date, the GIRK channels specifically coupled to 5-HT_{1A} receptors have not been identified. On the other hand, activation of 5-HT_{1A} receptors has also been shown to inhibit Ca²⁺ currents in several neuronal types [42, 43].

Regarding enzyme activities controlled by 5-HT_{1A} receptors, adenylyl cyclase and phospholipase C have been extensively investigated. As with all 5-HT₁ receptors, the 5-HT_{1A} receptor is negatively coupled to adenylyl cyclase [6, 44]. Pertussis toxin-sensitive inhibition of cAMP production in response to 5-HT_{1A} receptor stimulation has been described in a large number of cell types and cell lines. In contrast, activation of adenylyl cyclase by 5-HT_{1A} receptor stimulation is more controversial. Indeed, this response could reflect the stimulation of other types of 5-HT receptors, such as the 5-HT₇ receptor, for which many currently available 5-HT_{1A} receptor agonists have some affinity (notably 8-OH-DPAT). In recombinant systems, the positive coupling of 5-HT_{1A} receptors to cAMP production has been shown only in cells that express the AC2 form of adenylyl cyclase [45].

In addition to adenylyl cyclase, 5-HT_{1A} receptors have also been shown to modulate phosphatidylinositol-specific phospholipase C (PI-PLC) and protein kinase C activities in recombinant cell lines [46]. However, such couplings have never been demonstrated in brain tissues. Finally, 5-HT_{1A} receptor stimulation can also activate ERK Map kinases in recombinant CHO cells, through a complex signaling pathway, and regulate cell proliferation [6] and neurogenesis [47].

2 - 4 - Functional Implications

Widely distributed throughout the CNS, 5-HT_{1A} receptors are understandably implicated in a large number of physiological and behavioural processes, but notably in the regulation of (i) the cardiovascular system [48], (ii) neuroendocrine responses, such as the secretion of adrenocorticotrophic hormone (ACTH) [49, 50], (iii) body temperature [51], (iv) sleep states [52], (v) neurogenesis [47] and (vi) mood [53, 54]. The generation and phenotypic characterization of 5-HT_{1A} receptor knockout mice has supported the hypothesis that 5-HT_{1A} receptors play a role in anxiety and depression. Receptor-deficient animals have an increased tendency to avoid a novel and fearful environment and to escape a stressful situation, suggestive of increased anxiety and sensitivity to stress [55]. Indeed, 5-HT_{1A} receptor knockout mice exhibit more intense anxiety-like behavior in the plus maze, open field and conflict tests compared to wild-type mice. However, knockout animals are less immobile in the forced swim test and the tail suspension test than wild-type controls. Recent studies using selective regional rescue of the receptor in 5-HT_{1A} knockout mice led to the conclusion that postsynaptic 5-HT_{1A} receptors play a key role in the knockout-associated changes in anxiety-like behavior (see references in [53]). These results indicate that the targeted disruption of the 5-HT_{1A} receptor gene causes heritable perturbations in the serotonergic regulation of emotional state [56, 57].

2 - 5 - Disease Targets and Therapeutic Perspectives

In line with the data obtained in knockout mice, 5-HT_{1A} receptor ligands have been developed for treating anxiety and depression. The azapirone derivative buspirone was the first of a family of 5-HT_{1A} receptor agonists developed for the treatment of anxiety [58 - 60]. These psychoactive agents have both anxiolytic- and antidepressant-like effects in rodent behavioural assays [36, 61]. They exhibit the properties of full agonists at 5-HT_{1A} autoreceptors within the dorsal raphe nucleus and act generally as partial agonists at postsynaptic 5-HT_{1A} receptors, notably in the hippocampus [25].

The delay in onset of therapeutic benefit consistently observed after starting treatment with a 5-HT_{1A} receptor agonist (e.g. buspirone) or a selective serotonin reuptake inhibitor (SSRI) antidepressant has been attributed to slowly developing adaptive changes in 5-HT_{1A} autoreceptors. Many attempts have been made to enhance the therapeutic efficacy and to shorten the onset of action of 5-HT_{1A} psychoactive agents by blocking selectively 5-HT_{1A} autoreceptor-mediated inhibitory feedback (thereby enhancing 5-HT release at postsynaptic sites) without affecting postsynaptic 5-HT_{1A} heteroreceptors. However, to date, the selective and silent antagonists that have been synthesized do not discriminate between 5-HT_{1A} autoreceptors in anterior raphe nuclei and postsynaptic 5-HT_{1A} heteroreceptors in projection areas of serotonergic neurons. WAY 100635 was the first of these molecules having high selectivity and high affinity for 5-HT_{1A} receptors yet devoid of any intrinsic activity [50]. A few other molecules are now in development [3]. Currently, attempts are being made to elucidate the molecular mechanisms underlying the differential G protein- and

effector-coupling of 5-HT_{1A} auto- versus heteroreceptors, in order to find new targets for the design of compounds that would discriminate between them.

In addition to the treatment of diseases such as depression and anxiety, it has been suggested that 5-HT_{1A} receptor ligands may have therapeutic utility in drug addiction [62] as well as against the negative symptoms of schizophrenia [63]. Recent studies have also aimed to find a therapeutic potential for 5-HT_{1A} receptor antagonists in Alzheimer's dementia and other diseases associated with cognitive dysfunction. Indeed, 5-HT_{1A} receptor blockade has been shown to enhance signaling within heterosynaptic neuronal circuits involved in cognitive processes, thereby suggesting a novel therapeutic approach for reducing cognitive deficits [64].

3- 5-HT_{1B} RECEPTOR

3 - 1 - Cloning

The 5-HT_{1B} receptor was first identified as a specific binding site with high affinity for 5-HT but low affinity for spiperone [65]. In the rat brain, molecular cloning and characterization of a cDNA encoding the 5-HT_{1B} receptor allowed the demonstration that it corresponds to a 386 aminoacid long sequence with 7 hydrophobic (putative transmembrane) domains [66, 67]. Transient expression of this clone generated binding sites with high-affinity for [³H]5-HT and a pharmacological profile corresponding to that of the 5-HT_{1B} subtype in various cell types. In situ hybridization histochemistry revealed expression of 5-HT_{1B} receptor encoding mRNA within cells of the dorsal and median raphe nuclei, consistent with previous data showing that the 5-HT_{1B} receptor acts as an autoreceptor on 5-HT terminals in the rat brain. Interestingly, this function has also been ascribed to a closely related receptor, the 5-HT_{1D} type [68], and the existence of two terminal (5-HT_{1B/1D}) autoreceptors rather than only one has produced a complex and much debated story. It was first thought that the 5-HT_{1B} receptor is exclusively expressed in rodents (rat, mouse, hamster), and that the 5-HT_{1D} receptor represented its homologue in other species (human, bovine, dog, guinea pig [69]). However, although the two receptors have very similar pharmacological profiles, they are not identical. In particular, some β -adrenergic receptor antagonists were found to recognize with high affinity the 5-HT_{1B} but not the 5-HT_{1D} receptor. Such differences in the pharmacological profiles of the two receptors are in fact caused by a single amino acid in the 7th transmembrane spanning region: threonine³⁵⁵ in the non rodent species, versus asparagine³⁵⁵ in rodents [70, 71]. Because the brain distribution of the 5-HT_{1D} receptor in non rodent species and that of the 5-HT_{1B} receptor in rodents are similar, it was initially proposed that the two receptors were in fact species homologues of the same receptor [69]. However, further studies demonstrated that the so-called 5-HT_{1D} receptor in human is a complex of two subtypes, 5-HT_{1D α} and 5-HT_{1D β} , encoded by distinct genes it is now clearly established that 5-HT_{1B} and 5-HT_{1D β} receptors are rodent and non rodent species homologues of the same receptor type, with 97% overall sequence homology [6, 72]. The gene encoding the 5-HT_{1D β /1B} receptor is located on chromosome 6q13 in human and on chromosome 9E in mice [73].

3 - 2 - Distribution

Regional Distribution of 5-HT_{1B} Receptor mRNA

In addition to serotonergic neurons in the dorsal and median raphe nuclei (see above), expression of 5-HT_{1B} receptor encoding mRNA was also detected in cells within the CA1 region of the hippocampus, the striatum, the layer 4 of the cerebral cortex and the cerebellum (Purkinje cells) [67].

In situ hybridization histochemistry also demonstrated the presence of 5-HT_{1B} receptor mRNA in rat trigeminal and dorsal root ganglia, in line with the well established existence of presynaptic 5-HT_{1B} receptors on (i) trigeminal fibers in the spinal caudal nucleus of the trigeminal nerve and (ii) primary afferent fibers in the dorsal horn of the spinal cord, respectively [74].

Subcellular Localization of 5-HT_{1B} Receptors

Specific antipeptide antibodies have been used for the immunohistochemical visualization of 5-HT_{1B} receptors in the rat brain. A dense, specific 5-HT_{1B} receptor-like immunoreactivity was found in the globus pallidus, the dorsal subiculum and the substantia nigra (Fig. 2). At the light microscope level, immunostaining was diffuse within the neuropil but absent from cell bodies [23], consistent with other data indicating the expression of the receptor on

Substantia Nigra



Globus Pallidus



Fig. (2). 5-HT_{1B} receptor immunostaining in the substantia nigra and the globus pallidus of the rat brain (from ref. [20]).

Immunoperoxidase-labeled coronal sections show that these two regions contain the highest density of 5-HT_{1B} receptors in brain.

axons and terminals and in contrast with 5-HT_{1A} receptors that are exclusively located in neuronal somas and dendrites [75]. Indeed, observations at the electron microscope level in the substantia nigra confirmed that immunoperoxidase staining corresponding to 5-HT_{1B} receptors was confined to fine unmyelinated axons and nerve terminals [76].

Regional Distribution of 5-HT_{1B} Receptors

5-HT_{1B} receptors are expressed in the CNS in both presynaptic and postsynaptic locations with respect to serotonergic neurons [77]. They are particularly concentrated in the basal ganglia (globus pallidus, substantia nigra) and the frontal cortex where they act as terminal autoreceptors.

When expressed by non-serotonergic neurons, they act as terminal heteroreceptors controlling the release of other neurotransmitters [78].

Outside the CNS, 5-HT_{1B} receptors are found on cerebral arteries and other vascular tissues. Peripheral 5-HT_{1B}-mediated effects of 5-HT have been described, such as contraction of rat caudal arteries, inhibition of noradrenaline release in vena cava and inhibition of plasma extravasation produced by trigeminal ganglion stimulation in guinea pigs and rats. Evidence has been reported that the latter effect in fact results from the presynaptic blockade of the release of vasoactive neuropeptides (substance P, calcitonin gene-related peptide) from perivascular trigeminal fibres.

3 - 3 - Coupling

The 5-HT_{1B} receptor has been shown to couple to G α i/G α o proteins in transfected cells. Like that already described for the 5-HT_{1A} receptor, stimulation of the 5-HT_{1B} receptor inhibits adenylyl cyclase activity in brain tissues such as the substantia nigra [79] and in transfected cells of the Ltk-, Cos-7 and Sf9 lines (see [6]). However, 5-HT_{1B} receptors have also been reported to mediate cAMP accumulation and activate PLC in transfected cells, and to control inwardly rectifying potassium channels [80]. In addition, recent studies showed that 5-HT_{1B} receptor stimulation can activate ERK in different cell lines (see [6]).

3 - 4 - Functional Implications

As expected for autoreceptors, presynaptic 5-HT_{1B} receptors play a key role in the control of the release of 5-HT from serotonergic projections in various brain and spinal cord areas. As terminal heteroreceptors, they also participate in local inhibitory controls of the release of other neurotransmitters, such as acetylcholine, glutamate, dopamine, noradrenaline, gamma-aminobutyric acid and neuropeptides [78]. On the other hand, 5-HT_{1B} receptors expressed by cerebral arteries and other vessels (meningeal arteries, coronary arteries, etc) mediate vasomotor (vasoconstrictor) effects of 5-HT.

5-HT_{1B} receptor knockout mice have been reported to be highly aggressive: when confronted with an intruder, mutant mice attack the intruder much faster and more intensely than wild-type mice do, suggesting the participation of 5-HT_{1B} receptors in aggressive behavior [73]. Indeed, serenic drugs aimed at reducing aggressiveness have been proposed based on their capacity to stimulate 5-HT_{1B} receptors (see below).

In addition, 5-HT_{1B} receptor knockout mice are more reactive, and less anxious than the wild-types [81].

Because pharmacological and genetic data supported the idea that 5-HT_{1B} receptors could play a role in alcohol preference in human and rodents, alcohol intake was assessed in 5-HT_{1B} knockout mice. However, the controversial results reported so far [82 - 84] are more in favour of the conclusion that the 5-HT_{1B} receptor gene is very probably not a key component in the genetic background underlying alcohol preference in rodents.

3 - 5 - Disease Targets and Therapeutic Perspectives

In the late eighties, several authors demonstrated that sumatriptan interacts selectively with 5-HT_{1B} and 5-HT_{1D} sites and suggested that these interactions may underlie its efficacy in the acute treatment of migraine [85, 86]. Consequently, a number of triptans were developed for treating this disease (rizatriptan, eletriptan, almotriptan, naratriptan, zolmitriptan, etc) (see Fig. 3) which all share 5-HT_{1B} and 5-HT_{1D} receptor agonist properties [87, 88]. Interestingly, the ergot alkaloids such as ergotamine and dihydroergotamine, which preceded triptans in antimigraine therapy, are also highly potent agonists at 5-HT_{1B} and 5-HT_{1D} receptors. In acute migraine treatment, both triptans and ergot alkaloids constrict meningeal vessels and inhibit trigeminal neurotransmission at both peripheral and central levels through their agonist action at local 5-HT_{1B/1D} receptors [89].

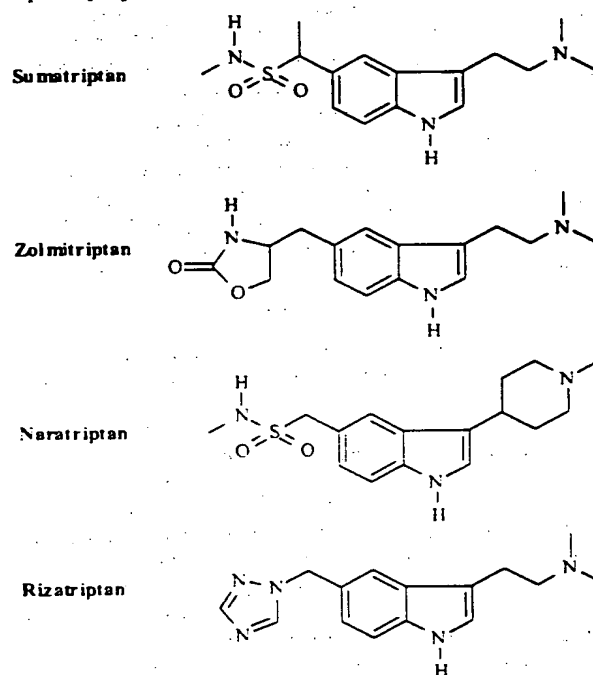


Fig. (3). Chemical structures of sumatriptan and other triptans.

5-HT_{1B} receptor agonists have anti-aggressive effects in individuals who show moderate to high levels of aggressiveness, consistent with the finding of high aggression in 5-HT_{1B} knockout mice. Thus, the aggression-inhibitory effects of anpirtoline can be blocked by

pretreatment with the potent 5-HT_{1B} receptor antagonist GR127935, thereby indicating that 5-HT_{1B} receptors mediate its effects [90]. Interestingly, a group of drugs sharing antiaggressive activity in rodents and subhuman primates, labelled "serenics", such as eltoprazine and fluprazine, have been developed. However, they lack selectivity for the 5-HT_{1B} receptor and antiaggressive efficacy could not be demonstrated in humans [91].

Recent data obtained with the selective 5-HT_{1B} receptor antagonist, NAS-181, have suggested that 5-HT_{1B} receptor blockade may have some potential in the treatment of cognitive deficits resulting from loss of cholinergic neurotransmission [92]. Consistent with this idea, evidence has been reported that the 5-HT_{1B} receptor inverse agonist, SB-224289, facilitates learning consolidation in an associative autoshaping learning task [93]. In addition, improved learning abilities have been described in 5-HT_{1B} knockout mice [94]. Whether the inverse agonist properties of some antipsychotics at cloned human 5-HT_{1B} and 5-HT_{1D} receptors [95] actually contribute to the therapeutic action of these drugs in schizophrenic patients is a relevant question to be addressed in future studies.

4 - 5-HT_{1D} RECEPTOR

4 - 1 - Cloning

The 5-HT_{1D} receptor gene was originally isolated by hybridization to a probe based on the RDC4 canine thyroid cDNA [96]. It was subsequently demonstrated that the pharmacologically defined human 5-HT_{1D} receptor in fact encompassed two distinct genes: 5-HT_{1Dα} and 5-HT_{1Dβ} [97 - 99]. The encoded proteins are now classified as 5-HT_{1D} and 5-HT_{1B} receptors, respectively, because of their high amino acid sequence identity (>95%) with their homologues in other species, such as rats and mice [100].

In man, the 5-HT_{1D} receptor gene is located on chromosome 1p34.3. It is intronless and encodes a protein of 377 amino acids.

4 - 2 - Distribution

In contrast to 5-HT_{1B} mRNA which is abundant in the CNS, 5-HT_{1D} mRNA is expressed at very low levels in brain tissues. 5-HT_{1D} mRNA hybridization signals have been predominantly described in caudate-putamen and cortical areas [74] and, to lower extents, in the olfactory tubercle, entorhinal cortex, dorsal raphe nucleus, cerebellum, spinal nucleus of the trigeminal nerve and in the trigeminal ganglion [101]. In line with these data, low densities of 5-HT_{1D} binding sites were found to be present in globus pallidus, ventral pallidum, caudate-putamen, subthalamic nucleus, entopeduncular nucleus, substantia nigra (reticular part), nuclei of the (normal and accessory) optic tract, different nuclei of the geniculate body and frontoparietal cortex [102]. However, the precise location of 5-HT_{1D} binding sites has yet to be established with really selective radioligands. Comparison of the respective distributions of encoding mRNA and 5-HT_{1D} binding sites revealed numerous mismatches throughout the rat brain, thereby suggesting that 5-HT_{1D} receptors are addressed to axonal

compartments where they probably act as presynaptic auto- and heteroreceptors modulating the release of serotonin and other neurotransmitters, respectively [74].

Interestingly, recent studies showed that 5-HT_{1B} and 5-HT_{1D} receptors can be physically associated. Both receptors would thus exist as monomers or homodimers when expressed alone, and as monomers or heterodimers when co-expressed in a given transfected cell line. Actually, gene expression studies have shown that there are brain regions where native 5-HT_{1B} and 5-HT_{1D} receptors are co-localized and where heterodimerization may occur under physiological conditions [103].

4 - 3 - Coupling

As for all other 5-HT₁ receptors, 5-HT_{1D} receptor stimulation has been shown to inhibit adenylyl cyclase activity through coupling with Gα_o/Gα_i proteins. In addition, 5-HT_{1D} receptors can regulate potassium and calcium channels [6].

4 - 4 - Functional Implications

One of the main functions of the 5-HT_{1D} receptor is to mediate the inhibitory control exerted by 5-HT on its own release in several brain regions, a function shared with 5-HT_{1B} receptors. However, the respective role of presynaptic 5-HT_{1B} and 5-HT_{1D} receptors in the feed-back inhibition of 5-HT release from serotonergic terminals is still a matter of debate. On the other hand, 5-HT_{1D} receptors have been shown to mediate the inhibitory influence of 5-HT on glutamate release from rat cerebellar synaptosomes [104]. In addition, 5-HT_{1D} receptor stimulation enhances GH secretion, possibly through the blockade of somatostatin release at the hypothalamic level [105]. The latter 5-HT_{1D} receptor-mediated effect is reduced in patients with episodic cluster headache, suggesting possible functional alterations of 5-HT_{1D} receptors associated with the disease [106].

4 - 5 - Disease Targets and Therapeutic Perspectives

Although currently available triptans do not discriminate between 5-HT_{1B} and 5-HT_{1D} receptors, it has been proposed that the 5-HT_{1D} receptor subtype plays a major role in the inhibitory effects of these drugs on meningeal neurogenic inflammation and trigeminal nociception associated with migraine attacks. In particular, selective 5-HT_{1D} receptor agonists, such as PNU 109291 and PNU 142633, are described as being more potent than sumatriptan in preventing plasma protein extravasation induced by electrical stimulation of the trigeminal ganglion [107, 108]. However, the therapeutic efficacy of selective 5-HT_{1D} receptor agonists in migraine in comparison to triptans with mixed 5-HT_{1B}/5-HT_{1D} receptor agonist properties remains to be established.

5- 5-HT_{1E} AND 5-HT_{1F} RECEPTORS

Among the 5-HT₁ receptors, both 5-HT_{1E} and 5-HT_{1F} receptor subtypes have been characterized by having high affinity for 5-HT but low affinity for 5-CT, in contrast with the other 5-HT₁ receptor subtypes which have high affinity for both agonists.

5 - 1 - Cloning and Distribution

Molecular cloning of the human and rat genes encoding the 5-HT_{1E} receptor was achieved in the early nineties [109 - 111]. This intronless gene, which is located on human chromosome 6q14-q15 [109], encodes a typical seven hydrophobic domain-endowed protein of 365 (human) or 366 (rat) amino acids [109, 112]. The mRNA encoding the 5-HT_{1E} receptor was found to be present in cortical areas, caudate, putamen and amygdala, areas known to contain 5-HT-insensitive 5-HT₁ binding sites [74].

The 5-HT_{1F} receptor encoding gene was first cloned in the mouse. It is also an intronless gene which codes for a 366 amino acid protein with seven hydrophobic, putative transmembrane, domains [113, 114]. In human, the 5-HT_{1F} gene is located on chromosome 3q11. Northern blot experiments showed that mRNA transcribed from the 5-HT_{1F} gene is expressed in brain but not in kidney, liver, spleen, heart, pancreas and testes in human [115]. In brain, in situ hybridization histochemistry allowed the detection of 5-HT_{1F} mRNA in the dorsal raphe nucleus, hippocampus, cerebral cortex, striatum, thalamus and hypothalamus [115].

5 - 2 - Coupling

Only a few studies have been devoted to identifying the signaling pathways downstream of the 5-HT_{1E} receptor. To date, it appears that this receptor is negatively coupled to adenylyl cyclase in BS-C-1 transfected cells, and stimulation by low concentrations of 5-HT actually decreased cAMP accumulation in these cells. However, high concentrations of the indolamine were found to activate adenylyl cyclase in BS-C-1 transfected cells [116].

5-HT_{1F} receptors are also negatively coupled to adenylyl cyclase in transfected cells, but some data also suggested that stimulation of these receptors can trigger PI-PLC activation [115].

5 - 3 - Disease Targets and Therapeutic Perspectives

While the functional role of 5-HT_{1E} receptors is not yet defined and selective ligands are still lacking, the situation is more advanced for the 5-HT_{1F} receptor. Indeed, this receptor is considered as a potential new target for the treatment of migraine [117]. Selective 5-HT_{1F} receptor agonists have been proposed for the treatment of this disease, without the side effects caused by the mixed 5-HT_{1B/1D} receptor agonists currently used for this indication [118]. Indeed, the second generation of triptans (e.g. zolmitriptan, rizatriptan, naratriptan) also have high affinity for the 5-HT_{1F} receptor. Compared to sumatriptan, the second-generation triptans have a higher oral bioavailability and longer plasma half-life but they also produce a strong presynaptic inhibition of the trigeminovascular inflammatory responses causally associated with migraine, which might implicate, at least partly, their agonist action at 5-HT_{1F} receptors. In line with this hypothesis, selective agonists at 5-HT_{1F} receptors, such as LY344864, were found to inhibit the trigeminovascular system without producing vasoconstriction [119]. Furthermore, recent studies demonstrated that selective 5-HT_{1F} receptor stimulation by LY334370 efficiently prevents dural inflammation in the neurogenic plasma protein extravasation model of migraine

and has a clear-cut clinical efficacy for the acute treatment of this disease [120].

FUTURE PROSPECTS

A large body of data has accumulated about the 5-HT₁ family of receptors since the discovery of the first ligand and radioligand with workable selectivity for one of its subtypes, i.e. the 5-HT_{1A} receptor agonist, 8-OH-DPAT and its tritiated derivative, [³H]8-OH-DPAT, two decades ago. Since that time, the most clinically significant progress has been the development of the mixed 5-HT_{1B/1D} receptor agonists for the acute treatment of migraine. In contrast, very little is known about the most recently discovered 5-HT₁ receptor subtypes, 5-HT_{1E} and 5-HT_{1F}. However, their specific distributions in the CNS suggest that drugs acting selectively at these sites might also have therapeutic potential. In addition, not all the pharmacological effects of 5-HT can be explained by its actions at the currently known receptors (especially in the spinal cord), and other receptor subtypes may yet be discovered with properties that would place them within the 5-HT₁ family. Finally, it should not be forgotten that new possibilities for subtle interventions aimed at a differential modulation of the functional status of 5-HT₁ receptors according to their pre- and/or post-synaptic localisation or even regional distribution are offered by the demonstration that 5-HT₁ receptor subtypes can (i) form heterodimers with pharmacological properties different from those of the constituting monomers, (ii) interact with modulatory proteins such as RGS (regulators of G protein signaling), and (iii) couple with different signaling pathways depending both on the cell type in which they are expressed and on the agonist selected for their stimulation. It is unlikely that the next twenty years will not yield a similar degree of progress and hopefully further therapeutic benefit.

ABBREVIATIONS

5-CT	=	5-Carboxamido-tryptamine
5-HT	=	5-Hydroxytryptamine (serotonin)
8-OH-DPAT	=	8-Hydroxy-2-(di-n-propylamino) tetralin
AC	=	Adenylyl cyclase
ACTH	=	Adrenocorticotrophic hormone
GIRK	=	G Protein-gated inwardly rectifying potassium channels
PI-PLC	=	Phosphatidylinositol-specific phospholipase C
RGS	=	Regulators of G protein signaling
WAY 100635	=	N-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl) cyclohexane carboxamide

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List of Drugs in Development for Neurodegenerative Diseases

Update June 2004

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Neurodegenerative diseases are an increasingly important issue in our society. There are, however, still many obstacles on the way to finding methods for cure. This table is intended to give an overview over neurodegenerative drugs that are currently in research and development in order to give the reader an idea about the complexity of drug discovery in this field. This table is intended as a pointer to drugs and it is recommended to obtain additional information from the internet to check for newest developments.

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
1	Discovery	University of South Florida	(-)-epigallocatechin-3-gallate	Neurodegenerative disease	IL synthesis modulator; Protein kinase C modulator; TACE modulator	Cell cycle inhibitor
2	Discovery	Fujimoto Seiyaku Co Ltd	(R)-(-)-BPAP	Neurodegenerative disease	Neurotransmitter modulator	Neuroprotectant
3	**Phase 1 Clinical	GlaxoSmithKline plc	644784	Pain; Schizophrenia	Cyclooxygenase 2 inhibitor	Antipsychotic; Analgesic
4	**Phase 1 Clinical	GlaxoSmithKline plc	742457	Alzheimers disease; Schizophrenia	5-HT 6 antagonist	Antipsychotic
5	**Phase 1 Clinical	GlaxoSmithKline plc	773812	Schizophrenia	5-HT antagonist; Dopamine modulator	Antipsychotic
6	**Phase 2 Clinical	Aventis Pharmaceuticals Inc	100907	Schizoaffective disorder; Anxiety disorder; Psychosis; Schizophrenia; Sleep disorder; Major depressive disorder	5-HT 2a antagonist	Antipsychotic
7	*Discontinued (Phase 2 Clinical)	Carlbotech Ltd	106362-32-7	HIV associated dementia; Neurodegenerative disease	peptide -T	Nootropic agent

* Changes made from last issue: ** newly added drug.

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	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
8	Discontinued	AstraZeneca plc	128298-28-2: Remacemide	Chorea Huntington. Cerebrovascular ischemia.	NMDA receptor antagonist	Neuroprotectant
9	*Launched (Phase 3 Clinical)	Cardinal Health Inc	14611-51-9: Selegiline: Zydys	Parkinsons disease: Cerebrovascular ischemia	MAO B inhibitor	DA enhancer
10	Discovery	National Institutes of Health	4-Cl-kynurenine	Neurodegenerative disease	NMDA receptor antagonist	Neuroprotectant
11	**Discovery	4SC AG	4SC. BK channel blockers	Incontinence: Asthma: Central nervous system disease	Ion channel modulator: Anti-inflammatory	Neuroprotectant
12	**Discovery	Sigma-Tau Ind Farm Riunite SpA	5-HT ₂ /dopamine D ₃ antagonists. Sigma-Tau	Psychosis: Schizophrenia	Dopamine D ₃ antagonist: 5-HT ₂ antagonist	Antipsychotic
13	**Discovery	Merck Sharp & Dohme Ltd	5-HT _{2a} antagonists. Merck & Co	Schizophrenia	5-HT _{2a} antagonist	Antipsychotic
14	**Discovery	NPS Allelix Corp	5-HT ₆ antagonists. Allelix	Psychiatric disorder: Schizophrenia	5-HT ₆ antagonist	Antipsychotic
15	**Discovery	SmithKline Beecham Pharmaceuticals	5-HT ₆ receptor antagonists. GlaxoSmithKline	Schizophrenia: Cognitive disorder: Major depressive disorder	5-HT ₆ antagonist	
16	**Clinical	Novartis AG	7B12	Spinal cord injury	NOGO antibody	Inhibition of exonal growth inhibitor
17	**Phase 1 Clinical	University of Pennsylvania	99mTc-Trodat-1, GE Healthcare	Parkinsons disease; Brain disease	SPECT contrast agent; Dopamine modulator	
18	Research Tool	Abbott Laboratories	A-134974	Epilepsy; Neurodegenerative disease	Adenosine kinase inhibitor	Anticonvulsant agent
19	Discovery	Abbott Laboratories	A-366833; A-35380	Alzheimers disease; Pain; Neurodegenerative disease; Nicotine use disorder: Anxiety disorder: Schizophrenia	Nicotinic ACh agonist, Neuronal nAChR ligand	Nootropic agent; Anxiolytic; Antipsychotic; Analgesic
20	Discontinued	Abbott Laboratories	A-72055	Neurodegenerative Disease	Muscarinic ACh agonist.	Nootropic agent
21	**Phase 1 Clinical	Ferrer Internacional SA	abaperidone	Schizophrenia	Dopamine D ₃ antagonist: Dopamine D ₂ antagonist: Antipsychotic: 5-HT _{2a} antagonist	Antipsychotic
22	**Phase 2 Clinical	Abbott Laboratories	ABT-089	Alzheimers disease: Schizophrenia: Attention deficit hyperactivity disorder	Nicotinic ACh modulator	Antipsychotic; Cognition enhancer
23	Discontinued	American Biogenetic Sciences Inc	ABS-205	Neurodegenerative disease: Cognitive disorder	Cell adhesion molecule modulator: Neuronal growth factor	Neuroprotectant

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
24	Discovery	ACADIA Pharmaceuticals Inc	AC-184897	Neurodegenerative disease: Carcinoma	Nuclear receptor agonists	Anticancer; Neuroprotectant
25	Discovery	ACADIA Pharmaceuticals Inc	AC-90222	Alzheimers Disease	Muscarinic M1 agonist	Nootropic agent
26	Discontinued	Cocensys Inc. Novartis	ACEA-1021	Epilepsy; Head trauma; Pain	NMDA/ Glycine antagonist	Neuroprotectant; Anticonvulsant
27	**Discovery	Synaptica Ltd	AChE peptide fragment (neurodegenerative disease). Synaptica	Alzheimers disease; Motor neurone disease; Parkinsons disease	Acetylcholinesterase modulator	Antiparkinsonian; Neuroprotectant
28	**Phase 1 Clinical	ACADIA Pharmaceuticals Inc	ACP-103	Psychosis; Schizophrenia	5-HT 2c receptor modulator; 5-HT 2a receptor modulator; 5-HT 2a antagonist	Antipsychotic
29	Phase 1 Clinical	Annovis Inc	ACPC. Annovis	Cerebrovascular ischemia; Neurological disease; Major depressive disorder	NMDA receptor partial agonist Antidepressant	Neuroprotectant
30	**Discovery	Prescient NeuroPharma Inc	ACPD analogs. 1GT	Epilepsy; Anxiety disorder; Cerebrovascular ischemia; Head injury	Metabotropic glutamate receptor 1 agonist; Metabotropic glutamate receptor 2 agonist	Neuroprotectant; Anxiolytic; Anticonvulsant agent
31	*Discontinued (Discovery)	National Institutes of Health	ADCI	Neurodegenerative disease	NMDA and sodium channel antagonist	Neuroprotectant; Anticonvulsant agent
32	**Discovery	ActinoDrug Pharmaceuticals GmbH	AD-GL0002	Parkinsons disease; Cancer; Cirrhosis	IL-6 synthesis inhibitor; Transcription factor inhibitor	Anticancer; Antiparkinsonian
33	Discovery	Aegera Therapeutics Inc	AEG-3482 series	Multiple sclerosis; Cerebrovascular ischemia; Cancer	Antiapoptotic	Neuroprotectant
34	**Discovery	Aeolus Pharmaceuticals Inc	AEOL-10150	Mucositis; Motor neurone disease; Cerebrovascular ischemia	Catalytic antioxidant	Neuroprotectant
35	**Discovery	Genentech Inc	agonist trkC monoclonal antibody, Genentech	Neuropathy	Protein tyrosine kinase modulator	Neuroprotectant
36	Discovery	AGY Therapeutics	AGY-110	Alzheimers disease; Schizophrenia; Major depressive disorder	Unclassified enzyme inhibitor	Nootropic agent
37	Discovery	AGY Therapeutics	AGY-207	Cerebrovascular ischemia	Unclassified enzyme inhibitor	Neuroprotectant
38	No Development Reported	Cortex/Alkermes	AK-275; Vasolex	Cerebral infarction; Ischemia	Calpain inhibitor	Neuroprotectant; Vasoprotectant
39	Phase 2 Clinical	VUFB	Alaptid	Alzheimers disease	Melanotropin-inhibiting factor (MIF)-1 analog	Nootropic agent

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
40	No Development Reported	NPS Allelix Corp	ALE-0540	Nervous system injury: Pain: Neurodegenerative disease	NGF antagonist	Neuroprotectant: Analgesic
41	**Discovery	Memory Pharmaceuticals Corp	alpha-7 partial agonists. Memory	Alzheimers disease: Schizophrenia: Central nervous system disease	Nicotinic ACh modulator	Nootropic agent
42	**Discovery	University of Queensland	alpha-conotoxins. University of Queensland	Neurological disease	Nicotinic ACh antagonist	Muscle relaxant
43	**Discovery	Isis Pharmaceuticals Inc	ALS antisense therapeutics. Isis	Motor neurone disease	Superoxide dismutase inhibitor. Antisense oligonucleotide inhibitor	Neuroprotectant
44	**Phase 3 Clinical	Harvard University/ Boston Life Sciences Inc	Altropane	Parkinsons disease: Attention deficit hyperactivity disorder	Dopamine transporter ligand. ¹²³ I labelled	Diagnostic/Imaging agent
45	**Discovery	University of Georgetown	Alzheimers disease therapeutic. Georgetown/ Samaritan	Spinal cord injury: Alzheimers disease: Neurodegenerative disease: Parkinsons disease: Dementia	CNS modulator	Neuroprotectant: Antiparkinsonian
46	**Discovery	Pharmexa A/S	Alzheimers vaccine (AutoVac), Pharmexa/ Lundbeck	Alzheimers disease	Vaccine: Target not disclosed	Neuroprotectant
47	Discovery	AMRAD Corp Ltd	AM-36	Cerebrovascular ischemia; Alzheimers disease, Spinal chord injury	Sodium channel blocker	Neuroprotectant; Antioxidant agent
48	Discovery	Annovis Inc	AMPA antagonists, Annovis	Epilepsy; Neurodegenerative disease; Schizophrenia; Cerebrovascular ischemia	AMPA receptor antagonist	Neuroprotectant; Antipsychotic; Anticonvulsant agent
49	**Discovery	Eli Lilly & Co	AMPA modulators, Lilly/NPS	Cognitive disorder	AMPA receptor modulator	Cognition enhancer
50	**Discovery	NV Organon	AMPA modulators, Organon	Alzheimers disease; Schizophrenia; Cognitive disorder	AMPA receptor modulator	Antipsychotic
51	**Discovery	Eisai Co Ltd	AMPA receptor antagonists (Multiple sclerosis), Eisai	Multiple sclerosis	AMPA receptor antagonist	Neuroprotectant
52	**Discovery	Yamanouchi Pharmaceutical Co Ltd	AMPA receptor antagonists. Yamanouchi	Central nervous system disease	AMPA receptor antagonist	Neuroprotectant
53	Discovery	University of California: Cortex: NV Organon: Servier	AMPAKINES	Dementia: Schizophrenia: Alzheimers disease	AMPA receptor modulator	Neuroprotectant; Antidepressant. Antipsychotic

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
54	Phase 1 Clinical	Axonyx Inc / Sero	Amyloid-inhibiting peptides	Alzheimers disease; Neurodegenerative disease	Beta amyloid generation inhibitor	Anti-amyloidogenic
55	Discontinued	Elan Pharmaceuticals Inc	AN-1792	Alzheimers disease	Synthetic beta amyloid; Vaccine	beta amyloid vaccine agonist
56	**Discovery	Fournier Pharma	anatibant	Allergic rhinitis; Asthma; Cerebrovascular ischemia; Head injury	Anti-inflammatory; Bradykinin B2 antagonist	Neuroprotectant
57	Discovery	Paracelsian Inc	Andrographolide	Neurodegenerative disease	Herbal product	Neuroprotectant; Anti-inflammatory
58	Phase 3 Clinical	Apollo Biopharmaceutics Inc / Wyeth	APBPI-124 / estrogen-like compounds	Alzheimers disease; Neurodegenerative disease; Parkinsons disease; Cerebrovascular ischemia	Estrogen modulator	Neuroprotectant; Antiparkinsonian
59	**Phase 2 Clinical	Britannia Pharmaceuticals Ltd	apomorphine (nasal; ED), Britannia	Erectile dysfunction; Parkinsons disease	Dopamine agonist	Antiparkinsonian; Apomorphine modulator
60	**Discovery	Merck Sharp & Dohme Ltd	apopain inhibitors, Merck Sharp	Neurodegenerative disease	Cysteine protease inhibitor	Apoptosis inhibitor
61	No Development Reported	ImmunoGen Inc	apoptosin	Neurodegenerative disease		Apoptosis modulator
62	No Development Reported	Oregon Health Sciences University	Aptiganel	Neurodegenerative disease; Parkinsons disease; Cerebrovascular disease; Cerebrovascular ischemia; Brain injury	NMDA receptor antagonist, Ionotropic glutamate receptor antagonist	Neuroprotectant; Antiparkinsonian
63	Discovery	Arena Pharmaceuticals Inc	AR-139525	Neurodegenerative disease; Parkinsons disease	Unspecified GPCR antagonist	Neuroprotectant; Antiparkinsonian
64	Discontinued	Fisons plc	AR-15896; lanicemine	Cerebral infarction; Ischemia	NMDA receptor antagonist	Neuroprotectant
65	Discovery	AstraZeneca plc	AR-A-008055	Neurotoxicity, drug-induced; Neurodegenerative disease	GABA A agonist	Neuroprotectant
66	*Launched (Phase 3 Clinical)	Eisai/Pfizer Inc	Aricept (Donepezil) vs. a-Tocopherol	Neurodegenerative disease; Alzheimers disease	Acetylcholinesterase inhibitor	Neuroprotectant; Cognition enhancer
67	Research Tool	AstraZeneca plc	AR-R-17779	Alzheimers disease; Neurodegenerative disease; Anxiety disorder	ACh agonist	Nootropic agent; Anxiolytic
68	No Development Reported	AstraZeneca plc	AR-R18565	Ischemia	Calcium channel blocker	Vasodilatory agent

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
69	No Development Reported	Array BioPharma Inc	ARRY-142886	Neurodegenerative disease	Protein kinase inhibitor; Mek protein kinase inhibitor	Neuroprotectant
70	Discovery	AlphaRx Inc	ARX-2000; -2001; -2002; AlphaRx	Inflammation; Neurodegenerative disease; Immune deficiency	Immunomodulators	Immunostimulant
71	**Phase 3 Clinical	NV Organon	asenapine	Psychosis; Schizophrenia	Dopamine D1 antagonist; Dopamine D2 antagonist; 5-HT 2a antagonist	Antipsychotic
72	Discovery	Serono SA	AS-600292; AS-004509; AS-601245	Chronic obstructive pulmonary disease; Inflammation; Inflammatory bowel disease; Multiple sclerosis; Neurodegenerative disease; Rheumatoid arthritis; Asthma; Central nervous system disease; Ischemia	Jun N terminal kinase modulator; Jun N terminal kinase-2 inhibitor; Jun N terminal kinase-3a inhibitor	Vasoprotectant; Anti-inflammatory
73	**Discovery	Avigen Inc	AV-201	Parkinsons disease	Dopamine synthesis modulator; Adeno-associated virus based gene therapy	Antiparkinsonian
74	**Phase 3 Clinical	Center for Neurologic Study	AVP-923	Neuropathic pain; Pain; Mood disorder; Cough	NMDA receptor antagonist	Antitussive; Analgesic; Neuroprotectant
75	**Discovery	Childrens Hospital of Boston	Axogenesis Factor 1; Boston Life Sciences	Spinal cord injury; Glaucoma; Motor neurone disease; Neurodegenerative disease; Cerebrovascular ischemia	NGF agonist	Neuroprotectant
76	No Development Reported	Regeneron Pharmaceuticals Inc	Axokine	Huntingtons chorea; Motor neurone disease; Neurodegenerative disease	CNTF agonist	Metabolic modulator
77	**Discovery	Acorda Therapeutics Inc	axonal guidance proteins; Acorda	Spinal cord injury; Parkinsons disease	Cell adhesion molecule modulator; Antiparkinsonian	Neuroprotectant
78	No Development Reported	Asahi Kasei Corp	AZ-36041	Alzheimers disease; Neurodegenerative disease	Reduction of amyloid beta	Neuroprotectant
79	*Discovery	AstraZeneca plc	AZD-0328	Alzheimers disease; Cognitive disorder	5-HT 3 agonist; Nicotinic ACh agonist	Nootropic agent; Anxiolytic
80	Discovery	BioAxone Therapeutique Inc	BA-1016	Neurodegenerative disease; Cerebrovascular ischemia; Cancer	Rho kinase inhibitor	Anticancer; Neuroprotectant

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
81	**Phase 1 Clinical	Bayer AG	BAY-38-7271	Pain: Cerebrovascular ischemia; Brain injury	Cannabinoid agonist	Neuroprotectant
82	No Development Reported	Bayer AG	BAY-X-9227	Neurodegenerative disease	Potassium channel activator	Neuroprotectant
83	No Development Reported	Russian Academy Medical Science	BD-1054	Alzheimers disease: Neurodegenerative disease		Nootropic agent
84	**Discovery	Toyama Chemical Co Ltd	benzothiophene derivatives (Alzheimers disease). Toyama	Alzheimers disease	benzothiophene derivatives	Neuroprotectant; Nootropic agent
85	**Phase 1 Clinical	Purdue Neuroscience Corp	besonprodil	Epilepsy; Pain; Parkinsons disease; Cerebrovascular ischemia	NMDA receptor antagonist	Analgesic; Antiparkinsonian; Anticonvulsant agent
86	Discontinued	Sankyo Co Ltd	BGC-20-1178	Neurodegenerative disease	Beta amyloid modulator	Nootropic agent
87	**Phase 1 Clinical	BIAL Group	BIA-3-202	Parkinsons disease	COMT inhibitor	Antiparkinsonian
88	**Phase 3 Clinical	Solvay SA	bifeprunox	Parkinsons disease; Psychosis; Schizophrenia	Dopamine D2 agonist; 5-HT 1a agonist	Antiparkinsonian
89	**Phase 2 Clinical	Boehringer Ingelheim Corp	BIII-890-CL	Pain; Cerebrovascular ischemia	Sodium channel blocker	Neuroprotectant
90	Discontinued	Boehringer Ingelheim Corp	BIMU-8	Neurodegenerative disease	5-HT4 agonist	Nootropic agent
91	Discovery	Boston Life Sciences Inc	BLS-602; BLS-605	Neurodegenerative disease; Parkinsons disease	DA transporter inhibitor	Neuroprotectant; Antiparkinsonian
92	**Phase 3 Clinical	Dainippon Pharmaceutical Co Ltd	blonanserin	Psychosis; Schizophrenia	5-HT 2 antagonist; Dopamine D2 antagonist	Antipsychotic
93	Discontinued	Bristol-Myers Squibb Co	BMS-181100	Schizophrenia, Psychosis	Sigma opioid antagonist, 5-HT 1a agonist	Antipsychotic
94	Discontinued	Bristol-Myers Squibb Co	Brasofensine	Parkinsons disease	Dopamine uptake inhibitor	Antiparkinsonian
95	No Development Reported	Pharm-Eco Laboratories Inc	Breflate	Neurodegenerative disease	Brefeldin A prodrug	Nootropic agent
96	Discovery	National Institutes of Health	BTG-A derivatives	Neurodegenerative disease	Nicotinic ACh modulator; Muscarinic ACh modulator	Nootropic agent
97	**Discovery	Knoll Ltd	BTS-72664	Epilepsy; Migraine; Cerebrovascular ischemia		Neuroprotectant; Analgesic; Anticonvulsant agent
98	**Discovery	Biovitrum AB	BVT-2989	Central nervous system disease		Neuroprotectant

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
99	**Discovery	OXIS International Inc	BXT-51072	Chronic obstructive pulmonary disease; Inflammatory bowel disease; Asthma; Restenosis; Ulcerative colitis; Cerebrovascular ischemia; Respiratory distress syndrome	Glutathione modulator	Neuroprotectant; Vasoprotectant
100	**Discovery	BioCryst Pharmaceuticals Inc	C1s inhibitors. 3-Dimensional Pharmaceuticals/ BioCryst	Inflammation; Myocardial infarction; Systemic lupus erythematosus; Autoimmune disease; Cerebrovascular ischemia; Respiratory distress syndrome	Anti-inflammatory; Serine protease inhibitor; Complement cascade inhibitor	Neuroprotectant; Cardioprotectant; Vasoprotectant
101	No Development Reported	Roche	C60 fullerenes	Neurodegenerative disease; Cerebrovascular ischemia; Head injury	Free radical scavenger	Neuroprotectant
102	**Discovery	Senju Pharmaceutical Co Ltd	calpain inhibitors. Senju Pharmaceutical	Nervous system injury; Muscular dystrophy; Neurodegenerative disease; Cataract; Cerebrovascular ischemia	Calpain inhibitor	Neuroprotectant
103	**Discovery	Genentech Inc	cardiotrophin-1	Glaucoma; Huntingtons chorea; Motor neurone disease; Uveitis; Cardiovascular disease	Cytokine, growth factor for myocytes	Growth factor
104	No Development Reported	Aventis	CAS-493; Aloracetam	Alzheimers disease		Nootropic agent
105	**Discovery	Sunesis Pharmaceuticals Inc	caspase inhibitors. Sunesis	Inflammation; Neurodegenerative disease; Cardiovascular disease	Caspase inhibitor; Antiapoptotic	Nootropic agent; Anti-inflammatory; Cardiovascular agent
106	**Discovery	Yamanouchi Pharmaceutical Co Ltd	caspase-3 inhibitors. Yamanouchi	Alzheimers disease; Liver disease; Myocardial infarction; Parkinsons disease; Cerebrovascular ischemia	Caspase inhibitor; Antiapoptotic	Neuroprotectant; Cardioprotectant; Antiparkinsonian
107	**Discovery	Cognitive Pharmaceuticals Ltd	CDD-0304	Alzheimers disease; Schizophrenia	Muscarinic M1 agonist	Nootropic agent
108	**Discovery	Novo Nordisk A/S	CEE-03-310	Alcoholism; Schizophrenia; Sleep disorder; Drug dependence	Dopamine D1 antagonist	Antipsychotic

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
109	**Discovery	Novo Nordisk A/S	CEE-05-320	Schizophrenia; Sleep disorder; Tardive dyskinesia; Drug dependence	Dopamine D1 antagonist	Antipsychotic
110	*Launched (Phase 3 Clinical)	Pfizer/Pharmacia; NIA: GD Searle & Co	Celecoxib	Alzheimers disease	Cox-2 antagonist	Neuroprotectant; Anti-inflammatory
111	**Phase 2 Clinical	Titan Pharmaceuticals Inc	cell therapy (dopamine producers: Parkinsons). Titan/Schering AG	Parkinsons disease	Dopamine agonist	Anticancer; Neuroprotectant; Antiparkinsonian
112	Phase 3 Clinical	Cephalon	CEP-1347	Parkinsons Disease	MAP kinase inhibitor	Neuroprotectant
113	Discovery	Cephalon Inc	CEP-3122	Alzheimers disease; Neurodegenerative disease; Cerebrovascular ischemia	Calpain inhibitor	Neuroprotectant
114	Discovery	Cephalon Inc	CEP-4143	Neurodegenerative disease	Calpain inhibitor	Neuroprotectant
115	Discontinued	LEO Pharma A/S	CEP-4186	Alzheimers disease; Acute myelogenous leukemia; Neurodegenerative disease; Carcinoma	Vitamin D3 agonist	Anticancer; Neuroprotectant
116	Discontinued	Cephalon Inc	CEP-751	Neurodegenerative disease; Prostate tumor	NGF antagonist; Protein tyrosine kinase inhibitor	Anticancer
117	Discontinued	Stem Cells Inc	CERE-20	Parkinsons disease	Growth factor agonist; Adeno-associated virus based gene therapy	Antiparkinsonian
118	**Discovery	University of Washington	CERE-120	Parkinsons disease; Neurological disease	Growth factor agonist; Adeno-associated virus based gene therapy; Ret tyrosine kinase receptor stimulator	Antiparkinsonian
119	**Discovery	The Salk Institute for Biological Studies	CERE-130	Motor neurone disease	Insulin-like growth factor agonist; Adeno-associated virus based gene therapy	Neuroprotectant
120	Discontinued	Novartis AG	CGP-35348	Epilepsy; Neurodegenerative disease	GABA B antagonist	Anticonvulsant agent
121	Phase 1 Clinical	Chiesi Farmaceutici SpA	CHF-2060	Neurodegenerative disease; Cognitive disorder; Senile dementia	Acetylcholinesterase inhibitor	Neuroprotectant; Cognition enhancer
122	**Phase 1 Clinical	Chiesi Farmaceutici SpA	CHF-3381	Epilepsy; Pain; Parkinsons disease; Cerebrovascular ischemia	MAO A inhibitor; MAO B inhibitor; NMDA receptor antagonist	Neuroprotectant; Analgesic; Antiparkinsonian; Anticonvulsant agent

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
123	**Research Tool	University of Oregon	cinnamide-based NMDA antagonists, CoCensys	Ischemia; Neurological disease; Injury: Head injury	NMDA receptor antagonist	Neuroprotectant
124	**Discovery	INSERM	ciproxifan	Epilepsy; Alzheimers disease; Dementia	Histamine H3 antagonist	Anticonvulsant agent
125	**No Development Reported	Chong Kun Dang Pharmaceutical Corp	CKD-705	Hypertension; Anxiety disorder; Parkinsons disease	Dopamine beta hydroxylase inhibitor; 5-HT release inhibitor	Antihypertensive; Anxiolytic; Antiparkinsonian
126	Discovery	Cogent Neuroscience Inc	CNIC-568	Neurodegenerative disease; Cerebrovascular ischemia	Unspecified vector based gene therapy	Neuroprotectant
127	Discontinued	CeNeS Pharmaceuticals Inc	CNS-1044	Neurodegenerative disease; Cerebrovascular ischemia	NMDA receptor antagonist	Neuroprotectant
128	No Development Reported	CeNeS Pharmaceuticals Inc	CNS-2103	Neurodegenerative disease	Calcium channel blocker	Neuroprotectant
129	No Development Reported	CeNeS Pharmaceuticals Inc	CNS-5065	Neurodegenerative disease	NMDA receptor antagonist	Neuroprotectant
130	Discontinued	Ryan Pharmaceuticals Inc	Coenzyme Q10;	Cerebrovascular ischemia	Apoptosis inhibitor	Neuroprotectant
131	**Clinical	ReGen Therapeutics plc	Colostrinin	Alzheimers disease	Amyloid protein deposition inhibitor; Proline rich peptide from colostorinin	Immunomodulator; Antioxidant agent
132	No Development Reported	Pfizer Inc	CP-132484	Neurodegenerative disease	5-HT 2 agonist	Neuroprotectant
133	No Development Reported	Pfizer Inc	CP-283097	Neurodegenerative disease	NMDA receptor antagonist	Neuroprotectant
134	**Discovery	Pfizer Inc	CP-465022	Epilepsy; Parkinsons disease; Ischemia	AMPA receptor antagonist	Antiparkinsonian; Anticonvulsant agent
135	*No Development Reported (Discovery)	Questcor Pharmaceuticals Inc	CPC-304	Neurodegenerative disease; Alzheimers disease; Cerebrovascular ischemia	Calcium channel blocker	Neuroprotectant
136	Phase 2 Clinical	Cortex Pharmaceuticals Inc	CX-516	Cognitive disorder; Alzheimers disease	Ampa receptor modulator	Neuroprotectant
137	Phase 1 Clinical	NIMH	Cyclophosphamide	Alzheimers disease; Neurodegenerative disease	Immunomodulator; Alkylating agent	Neuroprotectant; Anti-inflammatory
138	Discovery	Maas Biolab LLC	Cyclosporin A	Alzheimer disease; Parkinsons disease; ALS; Huntingtons disease	Immunomodulator; Calcineurin inhibitor	Neuroprotectant; Anti-inflammatory
139	Discontinued	Servier	Dabelotine	Alzheimers disease; Dementia	Adrenoceptor agonist; Vasopressin agonist	Nootropic agent

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
140	**Discovery	DarPharma Inc	DAR-201	Parkinsons disease; Schizophrenia; Attention deficit hyperactivity disorder	Dopamine D1 agonist	Antipsychotic; Antiparkinsonian
141	Research Tool	Suntory Ltd	DCG-IV	Neurodegenerative disease	Glutamate receptor agonist at mGlu-R group II receptors; Antagonist at mGlu-R group III receptors	Neuroprotectant
142	Discovery	DiverDrugsSL	DD-20207	Alzheimers disease; Parkinsons disease	NMDA receptor modulator	Analgesic; Antiparkinsonian
143	Discovery	Memorial Sloan-Kettering Cancer Center	Dehydroascorbic acid	Alzheimers disease; Neurodegenerative disease; Parkinsons disease; Cerebrovascular ischemia	Antioxidant agent	Neuroprotectant; Anti-inflammatory
144	**Phase 1 Clinical	NPS Pharmaceuticals Inc	delucemine. NPS 1506	Cerebrovascular ischemia; Major depressive disorder	NMDA open channel blocker	Neuroprotectant; Antidepressant
145	Discontinued	Hebrew University	dexanabinol	Cognitive disorder; Brain injury	NMDA receptor antagonist; TNF- α inhibitor; Free radical scavenger	Neuroprotectant
146	Phase 1 Clinical	Pierre Fabre SA / Reckitt & Colman plc	Dexefaroxan	Alzheimers disease	Imidazoline receptor antagonist; Alpha 2 adrenoceptor antagonist	Neuroprotectant
147	**Phase 2 Clinical	Purdue Research Foundation	dihyrexidine	Parkinsons disease; Schizophrenia	Dopamine D1 agonist	Antiparkinsonian
148	Discovery	Schering AG	Dihydroquinolines	Neurodegenerative disease	NO synthesis inhibitor	Neuroprotectant
149	No Development Reported	SIR International	Diperdipine	Neurodegenerative disease; Cerebral infarction; Cerebrovascular disease; Cerebrovascular ischemia	Calcium channel blocker	Antihypertensive
150	Research Tool	Merck & Co Inc	dizocilpine	Epilepsy; Neurodegenerative disease; Cognitive disorder	NMDA channel blocker	Anticonvulsant agent
151	Discontinued	Bristol-Myers Squibb Co	DMP-543	Alzheimers disease	Potassium channel blocker	Neuroprotectant
152	**Discovery	Novasite Pharmaceuticals Inc	dopamine D1 receptor agonists (schizophrenia), Novasite	Parkinsons disease; Schizophrenia	Dopamine D1 agonist	Antiparkinsonian
153	**Discovery	SmithKline Beecham plc	dopamine D3 antagonists. GlaxoSmithKline	Psychosis; Schizophrenia; Cocaine addiction	Dopamine D3 antagonist	Antipsychotic

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
154	**Discovery	Memory Pharmaceuticals Corp	dopamine D5 receptor modulators. Memory	Parkinsons disease	Dopamine D5 receptor modulator	Antiparkinsonian
155	**Discovery	Organix Inc	dopamine transporter ligand. Organix	Parkinsons disease; Schizophrenia; Cocaine addiction	Dopamine transporter inhibitor	Antipsychotic; Antiparkinsonian
156	Discovery	D-Pharm Ltd	DP-103	Nervous system inflammation		Anti-inflammatory
157	Discovery	D-Pharm Ltd	DP-109	Neurodegenerative disease	Chelating agent; Apoptosis modulator	Neuroprotectant
158	*Phase 2 Clinical (Discovery)	D-Pharm Ltd	DP-b99	Cerebrovascular ischemia. Epilepsy	Chelating agent. Calcium metabolism modulator	Neuroprotectant. Anticonvulsant agent
159	Discontinued	Mitsubishi-Tokyo Pharmaceuticals Inc	DPP-225	Alzheimers disease	5-HT antagonist	Neuroprotectant
160	**Discovery	Meiji Seika Kaisha Ltd	DR-2313	Cerebrovascular ischemia	PARP inhibitor	Neuroprotectant
161	**Phase 1 Clinical	Daiichi Seiyaku Co Ltd	DY-9760e	Cerebrovascular ischemia; Neurological disease	Calmodulin antagonist	Neuroprotectant; Protectant
162	Discovery	Korea Research Institute of Bioscience and Biotechnology	Dykellic acid	Immune disorder; Neurodegenerative disease; Cancer	MMP-5 inhibitor	Anticancer. Anti-apoptotic
163	**Phase 2 Clinical	Eisai Co Ltd	E-2007	Epilepsy; Multiple sclerosis; Parkinsons disease	AMPA receptor antagonist; Anticonvulsant agent	Neuroprotectant
164	**Phase 1 Clinical	Eisai Co Ltd	E-2051	Cerebrovascular ischemia	Calcium channel blocker	Neuroprotectant
165	Phase 1 Clinical	Eisai Co Ltd	E-2101	Neurodegenerative disease; Muscle hypertonia	5-HT 2 antagonist; 5-HT 1a antagonist	Centrally-acting muscle relaxant
166	**Discovery	Wyeth Research	E-selectin inhibitors, Wyeth	Reperfusion injury; Inflammation; Psoriasis; Rheumatoid arthritis; Cerebrovascular ischemia	E-Selectin antagonist	Neuroprotectant; Vasoprotectant; Anti-inflammatory
167	Discontinued	BTG International Ltd; Novartis	EAA-494; Midafotel	Epilepsy; Neurodegenerative disease; Cerebrovascular ischemia; Head injury	NMDA receptor antagonist	Neuroprotectant
168	Discovery	Wyeth Research	EAB-318	Epilepsy; Neurodegenerative disease; Cerebrovascular ischemia	NMDA receptor antagonist	Neuroprotectant; Anticonvulsant agent
169	**Discovery	NsGene A/S	ECT-AD	Alzheimers disease; Neurological disease	NGF agonist	Neuroprotectant; Growth factor
170	**Discovery	NsGene A/S	ECT-PD	Parkinsons disease	Neuronal growth factor receptor agonist	Neuroprotectant; Growth factor

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
171	Discontinued	Mitsubishi-Tokyo Pharmaceuticals Inc	edaravone	Cerebrovascular ischemia	Free radical scavenger	Neuroprotectant
172	Discovery	Universidad Complutense de Madrid	EF-7412	Neurodegenerative disease: Anxiety disorder, Depression	5HT-1A antagonist	Antidepressant; Anxiolytic
173	No Development Reported	EGIS Gyogyszergyar RT	EGIS-7444	Alzheimers disease: Neurodegenerative disease	NMDA receptor antagonist	Neuroprotectant
174	**Phase 3 Clinical	ExonHit Therapeutics SA	EHT-201, Pentoxifyllin	Motor neurone disease: Central nervous system disease	Vasodilator	Neuroprotectant
175	Phase 1 Clinical	ExonHit Therapeutics SA	EHT-202, FK-506	Neurodegenerative disease	T-cell inhibitor	Neuroprotectant
176	Discontinued	Synthelabo	Eliprodil	Motor neurone disease: Neurodegenerative disease: Cerebrovascular disease: Cerebrovascular ischemia: Head injury	NMDA receptor antagonist	Neuroprotectant
177	Discontinued	Knoll GmbH	emopamil	Migraine: Neurodegenerative disease: Cerebrovascular ischemia	5-HT 2 antagonist; 5-HT antagonist; Calcium channel blocker	Neuroprotectant; Vasodilatory agent
178	Discovery	University of Tennessee Memphis	EP-475	Neurodegenerative disease	Calpain inhibitor	Neuroprotectant
179	*Launched (Phase 2 Clinical)	ASAC Pharmaceutical International AIE	EQA-00; Anapsos, Polypodium extract	Multiple sclerosis	Immunomodulator	Immunomodulator, Nootropica agent
180	*Launched (Phase 3 Clinical)	ASAC Pharmaceutical International AIE	EQA-00; Anapsos	Alzheimers disease	Immunomodulator	Immunomodulator, Nootropica agent
181	No Development Reported	Kyowa Hakko Kogyo Co Ltd	ES-242-1	Neurodegenerative disease	NMDA receptor antagonist	Neuroprotectant
182	Phase 3 Clinical	NIA (National Institute of Aging)	Estrogen or Estrogen/ Progesterone	Alzheimer's Disease	Immunomodulator; Hormone	Neuroprotectant; Anti-inflammatory
183	**Discovery	MitoKor	estrogen analogs (ischemia), MitoKor	Myocardial infarction: Cerebrovascular ischemia	Estrogen modulator; Hormone	Neuroprotectant; Cardiovascular agent
184	No Development Reported	GD Searle & Co	ethanoanthracene derivatives	Neurodegenerative disease	Sigma opioid antagonist	Neuroprotectant
185	No Development Reported	Centre de Recherche Pierre Fabre	F-10981	Alzheimers disease: Neurodegenerative disease: Parkinsons disease	Alpha 2 adrenoceptor antagonist	Antiparkinsonian

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
186	Discovery	Tokyo Metropolitan Institute	F-2-CCG-I	Epilepsy; Neurodegenerative disease; Head injury	Metabotropic glutamate receptor modulator	Anticonvulsant agent
187	No Development Reported	Pharmacia & Upjohn Inc	FCE-29484A	Neurodegenerative disease; Parkinsons disease; Epilepsy		Antiparkinsonian; Anticonvulsant agent
188	No Development Reported	Pharmacia & Upjohn Inc	FCE-29642A	Neurodegenerative disease; Parkinsons disease; Epilepsy		Antiparkinsonian; Anticonvulsant agent
189	No Development Reported	Amgen Inc	FGF-9; rhuFGF-16	Multiple Sclerosis; Neurodegenerative disease	FGF-9 agonist; FGF-16 agonist	Neuroprotectant
190	No Development Reported	Amgen Inc	fibroblast growth factor, ersefermin	Multiple sclerosis; Neurodegenerative disease; Cerebrovascular ischemia	FGF-2 agonist	Neuroprotectant
191	**Phase 2 Clinical	Juvantia Pharma Ltd	fpamezole	Parkinsons disease	Alpha 2 adrenoceptor antagonist	Antiparkinsonian
192	**Discovery	Kosan Biosciences Inc	FK-520 analogs, Kosan	Neurological disease	NGF agonist	Immuno-suppressant
193	**Phase 2 Clinical	Fujisawa Pharmaceutical Co Ltd	FK-960	Alzheimers disease; Cognitive disorder	5-HT agonist	Nootropic agent
194	**Discovery	Pfizer Inc	FKBP inhibitors, Pfizer	Alzheimers disease; Neurodegenerative disease; Parkinsons disease; Peripheral neuropathy	Immunomodulator	Anti-inflammatory
195	**Phase 3 Clinical	Bristol-Myers Squibb Co	flindokalner	Cerebrovascular ischemia	Potassium channel activator	Neuroprotectant
196	**Phase 1 Clinical	Harvard University	Fluoratec	Parkinsons disease; Attention deficit hyperactivity disorder; Neurological disease	Dopamine uptake modulator	Antiparkinsonian
197	No Development Reported	Kirin Brewery Co Ltd	Formobactin	Neurodegenerative disease; Cerebrovascular ischemia	Free radical scavenger	Neuroprotectant
198	No Development Reported	Fisons plc	FPL-16283	Neurodegenerative disease	NMDA receptor antagonist	Neuroprotectant
199	**Discovery	Fujisawa Pharmaceutical Co Ltd	FR-210575	Cerebrovascular ischemia	Free radical scavenger	Neuroprotectant
200	*Discovery (No Development Reported)	Neurochem Inc	GAG mimetics	Alzheimers disease	Amyloid protein deposition inhibitor	Neuroprotectant
201	Discovery	Synaptica Ltd/ Sanochemia Pharmazeutika AG	Galantamine derivatives	Alzheimers disease	Acetylcholinesterase inhibitor	Nootropic agent; cognition enhancer

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
202	No Development Reported	GlaxoSmithKline plc	galdansetron	Neurodegenerative disease	5-HT 3 antagonist	Neuroprotectant
203	**Discovery	Elan Pharmaceuticals Inc	gamma-secretase inhibitors. Elan/Lilly	Alzheimers disease	Beta amyloid synthesis inhibitor. Gamma-secretase inhibitor. Aspartic protease inhibitor	Neuroprotectant
204	Phase 2 Clinical	Chiesi Farmaceutici SpA	ganstigmine	Alzheimers disease: Neurodegenerative disease: Cognitive disorder	Acetylcholinesterase inhibitor	Neuroprotectant
205	Discontinued	GlaxoSmithKline plc	gavestinel	Neurodegenerative disease: Cerebrovascular ischemia	Glycine antagonist	Neuroprotectant
206	Discovery	Genentech Inc	GDNF	Neurodegenerative disease: Parkinsons disease	Unspecific growth factor agonist	Antiparkinsonian
207	Phase 2 Clinical	Amgen Inc	GDNF; Liatermine	Motor neurone disease: Neurodegenerative disease: Parkinsons disease	Growth factor	Antiparkinsonian
208	**Discovery	Oxford BioMedica plc	gene therapy (ALS), Oxford BioMedica	Motor neurone disease	Viral vector based gene therapy	Neuroprotectant
209	**Discovery	Oxford BioMedica plc	gene therapy (Parkinsons disease), Oxford BioMedica	Parkinsons disease	Tyrosine hydroxylase modulator; Dopamine synthesis stimulant; Retrovirus based gene therapy	Antiparkinsonian; Dopamine modulator
210	Discovery	CeNeS Pharmaceuticals Inc, Acorda	GGF-2	Multiple sclerosis, Myasthenia gravis	NGF agonist, Growth factor	Neuroprotectant
211	Phase 2 Clinical	ViatraVIATRIS GmbH	GKE-841; retigabine	Epilepsy	GABA A agonist: Potassium channel activator	Anticonvulsant agent
212	No Development Reported	Allelix Neuroscience Inc	Glialines, Throphix	Alzheimers disease: Huntingtons chorea: Parkinsons disease	Cell therapy: Glial neurotrophic factors	Neuroprotectant; Antiparkinsonian
213	**Discovery	Glaxo Wellcome SpA	glycine antagonists. GlaxoSmithKline	Epilepsy: Pain: Schizophrenia: Cerebrovascular ischemia: Head injury	Glycine antagonist: NMDA receptor antagonist: Anticonvulsant agent	Neuroprotectant; Antipsychotic; Analgesic;
214	**Discovery	Eli Lilly & Co	glycine transporter inhibitors. Lilly	Schizophrenia	Glycine transport inhibitor	Antipsychotic
215	**Discovery	Allelix Neuroscience Inc	GlyT-1 inhibitors. NPS/Janssen	Schizophrenia: Dementia	Glycine modulator	Antipsychotic

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
216	*Clinical (Enrollment)	NINDS (National Institute of Neurological Disorders and Stroke)	GM-1 ganglioside	Neurodegenerative disease	Unclear mechanism	Neuroprotectant
217	Phase 2 Clinical	Fidia Farmaceutici	GM-1 ganglioside	Parkinsons disease	Unclear mechanism	Neuroprotectant
218	**Discovery	Parke-Davis & Co	GMC-1111	Parkinsons disease; Schizophrenia	Dopamine D2 agonist	Antiparkinsonian
219	No Development Reported	SICOR Inc	GP-14683	Epilepsy; Angina; Neurodegenerative disease	ARA-100 prodrug	Vasodilatory agent; Anticonvulsant agent
220	Discontinued	Guilford Pharmaceuticals Inc	GPI-1337	Neurodegenerative disease; Parkinsons disease	Neuroimmunophilin ligand	Neuroprotectant; Antiparkinsonian; Anti-inflammatory
221	*Phase 2 clinical (Discontinued)	Guilford Pharmaceuticals Inc, Symphony Neuro Development Co	GPI-1485	Parkinsons disease	Neuroimmunophilin	Antiparkinsonian; Anti-inflammatory
222	Research Tool	GlaxoSmithKline plc	GR-73632	Neurodegenerative disease	NK1 agonist	Neuroprotectant
223	Discontinued	GlaxoSmithKline plc	GR-89696	Neurodegenerative disease	Kappa opioid agonist	Neuroprotectant
224	Discovery	AstraZeneca plc	GSK-3 inhibitors	Alzheimers disease	Glycogen synthase kinase family inhibitor	Neuroprotectant
225	Discontinued	Gliatech Inc	GT-2342	Neurodegenerative disease	Histamine H3-ligand	Neuroprotectant
226	Discovery	GBtherapeutics Ltd	GT-715	Neurodegenerative disease	NO modulator	Neuroprotectant
227	Discovery	BTG International Ltd	GV-2400	Neurodegenerative disease; Cardiovascular disease; Cancer	HSV gene therapy	Neuroprotectant
228	Discontinued	EGIS Gyogyszergyar RT	GYKJ-52466	Alzheimers disease; Parkinsons disease; Epilepsy	AMPA receptor antagonist	Anticonvulsant agent; Antiparkinsonian
229	No Development Reported	American Cyanamid Co	HBNF	Hematological disease; Neurodegenerative disease	Heparin binding neurotrophic factor; FGF-8 agonist; Peptide	
230	Discovery	Hunter-Fleming Ltd	HF-0220	Cerebrovascular ischemia	7-hydroxysteroid pathway modulator	Neuroprotectant
231	**Discovery	Curis Inc	Hh agonists; Curis	Diabetic neuropathy; Infertility; Alopecia; Parkinsons disease; Bone disease; Neurological disease	Hedgehog agonist	Neuroprotectant; Antiparkinsonian
232	*Phase 2 Clinical (Phase 1 Clinical)	Aventis	HP-184	Spinal chord injury	Ion channel modulator; Acetylcholine release stimulator	Neuroprotectant

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
233	**Discovery	Tapestry Pharmaceuticals Inc	Huntingtons disease therapy. Tapestry	Huntingtons chorea	Gene therapy	Neuroprotectant
234	Discovery	Aegera Therapeutics Inc	IAP	Parkinsons disease. Multiple sclerosis. Cerebrovascular ischemia	Anti-apoptotic gene therapy	Neuroprotectant
235	**Phase 1 Clinical	ICAgen Inc	ICA-69673	Epilepsy; Pain; Anxiety disorder; Parkinsons disease; Arthritis	Ion channel modulator	Anxiolytic; Analgesic; Antiparkinsonian; Anticonvulsant agent
236	Discovery	Idun Pharmaceuticals Inc	IDN-6556	Neurodegenerative disease	Caspase inhibitor	Apoptosis inhibitor; Anti-inflammatory
237	**Research Tool	Synthelabo	ifenprodil	Schizophrenia; Cerebral infarction; Cerebrovascular ischemia	Noncompetitive NMDA antagonist	Neuroprotectant; Antipsychotic
238	Discovery	Neurocrine Biosciences Inc	IGF modulators. Neurocrine	Neurodegenerative disease; Central nervous system disease; Cerebrovascular ischemia	Insulin-like growth factor 1 agonist	Neuroprotectant; Antipsychotic
239	Discontinued	Pfizer Inc	Igmeline	Alzheimers disease	Sigma opioid agonist	Neuroprotectant
240	**Discovery	Prescient NeuroPharma Inc	IGT-440103	Cerebrovascular ischemia; Head injury	Metabotropic glutamate receptor agonist	Neuroprotectant
241	**Discovery	Hoechst Marion Roussel Inc	iloperidone	Psychosis; Schizophrenia	Dopamine D2 antagonist; 5-HT 2a antagonist	Antipsychotic
242	No Development Reported	Ortho Pharmaceutical Corp	Imidazole derivatives	Pain; Neurodegenerative disease	Alpha 3 adrenoceptor agonist	Analgesic
243	Discovery	Servier	Imidazolyl nitrones	Nervous system injury; Neurodegenerative disease	Free radical scavenger	Neuroprotectant; Antioxidant agent
244	**Discovery	Cytos Biotechnology AG	Immunodrug vaccines (Alzheimers disease). Cytos/ Novartis	Alzheimers disease	Vaccine against BA4 fragments	Neuroprotectant
245	**Phase 2 Clinical	Inotek Pharmaceuticals Corp	INO-1001	Nervous system injury; Reperfusion injury; Colitis; Sepsis; Multiple sclerosis; Myocardial infarction; Arthritis; Uveitis; Cerebrovascular ischemia; Diabetes mellitus; Diabetic complication	PARP inhibitor	Neuroprotectant

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
246	Discovery	Boston Life Sciences Inc	inosine. BLSI	Neurodegenerative disease	Adenosine precursor	Neuroprotectant
247	Phase 1 - 2 Clinical	NCRR	Interferon Alpha	Alzheimers disease: Dementia	Immunomodulator	Neuroprotectant; Anti-inflammatory
248	No Development Reported	Yeda Research & Development Co Ltd	Interleukin-2-like growth factor	Neurodegenerative disease	IL-2 agonist	Growth factor agonist
249	*Pre-registration (Phase 3 Clinical)	Research Triangle Institute	lometopane	Parkinsons disease	Dopamine uptake inhibitor. SPECT contrast agent	Neuroprotectant; Antiparkinsonian
250	Phase 2 Clinical	Nippon Chemiphar Co Ltd	lpenoxazone	Alzheimers disease; Neurodegenerative disease; Middle ear disease	NMDA receptor antagonist; Ionotropic glutamate receptor antagonist	Smooth muscle relaxantium
251	Discovery	Chronogen Inc	isp-1; clk-1	Neurodegenerative disease	Protein tyrosine kinase STY	Neuroprotectant
252	**Phase 2 Clinical	Kyowa Hakko Kogyo Co Ltd	istradefylline	Parkinsons disease; Major depressive disorder	Adenosine A2a antagonist	Antidepressant; Antiparkinsonian
253	**Discovery	Bristol-Myers Squibb Pharma Co	IT-657	Schizophrenia	Dopamine D2 antagonist; 5-HT 2a antagonist	Antipsychotic
254	No Development Reported	Aventis	itameline	Dementia, Alzheimers disease, Cognitive disorder	Muscarinic ACh agonist	Nootropic agent
255	**Discovery	Serono SA	JNK inhibitors, Serono	Chronic obstructive pulmonary disease; Inflammation; Inflammatory bowel disease; Multiple sclerosis; Neurodegenerative disease; Rheumatoid arthritis; Asthma; Central nervous system disease; Ischemia; Pulmonary fibrosis	Jun N terminal kinase modulator; Jun N terminal kinase-2 inhibitor; Jun N terminal kinase-3a inhibitor	Vasoprotectant; Anti-inflammatory
256	No Development Reported	Kyowa Hakko Kogyo Co Ltd	KF-17329	Neurodegenerative disease; Cerebrovascular ischemia		Neuroprotectant
257	*Discontinued	Krenitsky Pharmaceuticals Inc	KP-102	Neurodegenerative disease	NGF agonist	Neurotrophic agent
258	**Discovery	Kyorin Pharmaceutical Co Ltd	KRP-199	Cerebrovascular ischemia	AMPA receptor antagonist	Neuroprotectant
259	Discovery	Keryx Biopharmaceuticals Inc	KRX-411	Neurodegenerative disease	Protein kinase modulator	Neuroprotectant

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
260	Phase 2 Clinical	Kyowa Hakko	KW-6002: Istradefylline	Parkinsons disease: Major depressive disorder	Adenosine A2a antagonist	Neuroprotectant
261	No Development Reported	Merck & Co Inc	L-687306	Alzheimers disease	Muscarinic M1 agonist	Nootropic agent
262	Research Tool	Merck & Co Inc	L-687414	Epilepsy: Neurodegenerative disease	NMDA receptor antagonist	Anticonvulsant agent
263	Research Tool	Merck & Co Inc	L-689560	Neurodegenerative disease	NMDA receptor antagonist	Anticonvulsant agent
264	No Development Reported	Merck & Co Inc	L-701252	Alzheimers disease: Epilepsy: Cerebrovascular ischemia	NMDA receptor antagonist	Neuroprotectant: Anti-convulsant agent
265	**Phase 1 Clinical	Hebrew University of Jerusalem	ladostigil	Alzheimers disease	Acetylcholinesterase inhibitor: MAO B inhibitor	Neuroprotectant: Nootropic agent
266	**Phase 1 Clinical	GlaxoSmithKline plc	Lamictal XR	Epilepsy: Neuropathic pain	Sodium channel blocker: Glutamate release inhibitor	Neuroprotectant: Antidepressant: Antipsychotic: Anticonvulsant agent
267	*Launched (Phase 3 Clinical)	GlaxoSmithKline plc	lamotrigine	Neuropathy	Glutamate release inhibitor	Neuroprotectant: Anticonvulsant agent
268	Discovery	Louisiana University	LAU-0501	Alzheimers disease: Parkinsons disease	Cyclooxygenase 2 inhibitor	Anti-inflammatroy; Antiparkinsonian
269	**Discovery	Louisiana State University	LAU-8080	Cerebrovascular ischemia	PAF antagonist: Platelet aggregation inhibitor	Neuroprotectant
270	**Phase 3 Clinical	Scotia Holdings plc	LAX-101	Huntingtons chorea: Schizophrenia: Bipolar disorder: Major depressive disorder	Phospholipase inhibitor	Antidepressant: Antipsychotic
271	Discontinued	Roche	lazabemide	Alzheimers disease: Neurodegenerative disease: Parkinsons disease: Dementia	MAO B inhibitor	Antiparkinsonian
272	**Discovery	Oxford BioMedica plc	LentiVector	Unidentified: HIV infection: Motor neurone disease: Parkinsons disease: Asthma: Cystic fibrosis: Diabetes mellitus	EGF-, VEGF-agonist: Apoptosis antagonist	
273	Phase 2 Clinical	Spectrum Pharmaceuticals	Leteprinin	Parkinsons disease: Spinal chord injury	FGF agonist: NGF agonist	Nootropic agent: Antiparkinsonian
274	**Discovery	Renovis Inc	leukocyte trafficking (neuro-degenerative disease). Renovis	Neurodegenerative disease	leukocyte trafficking inhibitors	Neuroprotectant: Anti-inflammatory

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
275	Discovery	Fidia-Georgetown Institute for Neurosciences	LIGA-20	Neurodegenerative disease; Cerebrovascular ischemia	Excitatory amino acid antagonist	Neuroprotectant
276	**Discovery	OXIS International Inc	lipid soluble antioxidants. Oxis	Alzheimers disease; Parkinsons disease; Central nervous system disease	Antioxidant	Antiparkinsonian
277	**Discovery	University of Chicago	LXR agonists (Alzheimers disease). Anagen Therapeutics	Alzheimers disease	Liver X receptor agonist	Neuroprotectant
278	No Development Reported	Eli Lilly & Co	LY-178002	Inflammation; Neurodegenerative disease	Antioxidant	Anti-inflammatory; Immuno-suppressant
279	No Development Reported	Eli Lilly & Co	LY-233536	Neurodegenerative disease	Competitive NMDA antagonist	Antiparkinsonian; Anticonvulsant agent
280	No Development Reported	Eli Lilly & Co	LY-235959	Neurodegenerative disease	Competitive NMDA antagonist	Antiparkinsonian; Anticonvulsant agent
281	Discontinued	Eli Lilly & Co	LY-274614	Epilepsy; Alzheimers disease; Neurodegenerative disease; Opiate use disorder; Parkinsons disease; Dementia	NMDA receptor antagonist	Antiparkinsonian; Anticonvulsant agent
282	**Phase 2 Clinical	Eli Lilly & Co	LY-293558	Epilepsy; Pain; Migraine; Cerebral infarction; Cerebrovascular ischemia	AMPA receptor antagonist; Anticonvulsant agent	Neuroprotectant; Analgesic
283	*Research Tool (No Development Reported)	Eli Lilly & Co	LY-302427	Neurodegenerative disease	Metabotropic glutamate receptor modulator	Neuroprotectant
284	No Development Reported	Eli Lilly & Co	LY-354006	Alzheimers disease; Neurodegenerative disease	Muscarinic ACh modulator	Nootropic agent
285	Phase 2 Clinical	Eli Lilly & Co	LY-354740	Anxiety disorder	Metabotropic glutamate receptor 2 agonist	Anxiolytic; Anticonvulsant agent
286	Phase 1 Clinical	Eli Lilly & Co	LY-451395	Alzheimers disease; Neurodegenerative disease	AMPA receptor agonist	Neuroprotectant
287	**Discovery	Eli Lilly & Co	LY-483518	Alzheimers disease; Anxiety disorder; Psychosis; Schizophrenia; Cognitive disorder	5-HT 6 antagonist	Nootropic agent; Anxiolytic; Antipsychotic

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
288	**Discovery	MetaPhore Pharmaceuticals Inc	M-40401	Reperfusion injury; HIV infection; Parkinsons disease; Shock; Encephalitis	Viral replication inhibitor; Apoptosis inhibitor; Superoxide dismutase stimulator; HIV replication inhibitor	
289	Discovery	Mitsubishi-Tokyo Pharmaceuticals Inc	MCC-257	Diabetic neuropathy; Neurodegenerative disease	NGF agonist	Neuroprotectant
290	Discontinued	Mitsubishi-Tokyo Pharmaceuticals Inc	MCI-225	Alzheimers disease; Neurodegenerative disease; Depression	5-HT 3 antagonist; Norepinephrine uptake inhibitor	Antidepressant; Metabolic activator
291	No Development Reported	Hoechst Marion Roussel Inc	MDL-100748	Epilepsy; Neurodegenerative disease	NMDA/Glycine antagonist; Glycine antagonist	Anticonvulsant agent
292	Discontinued	Hoechst Marion Roussel Inc	MDL-101002	Neurodegenerative disease; Cerebrovascular ischemia; Septic shock	Free radical scavenger	Neuroprotectant; Antioxidant agent
293	No Development Reported	Hoechst Marion Roussel Inc	MDL-102288	Neurodegenerative disease	Glycine antagonist	Neuroprotectant
294	No Development Reported	Hoechst Marion Roussel Inc	MDL-105519	Neurodegenerative disease	Glycine antagonist; NMDA receptor antagonist	Neuroprotectant
295	No Development Reported	Hoechst Marion Roussel Inc	MDL-27266	Epilepsy; Neurodegenerative disease	Glycine antagonist; NMDA receptor antagonist	Ionotropic glutamate receptor antagonist; Anticonvulsant agent
296	Discontinued	Hoechst Marion Roussel Inc	MDL-28170	Alzheimers disease; Neurodegenerative disease	Cysteine protease inhibitor; Hydrolase inhibitor; Amyloid protein deposition inhibitor; Calpain inhibitor	Antiparasitic; Neuroprotectant
297	No Development Reported	Hoechst Marion Roussel Inc	MDL-29951	Epilepsy; Neurodegenerative disease	NMDA/Glycine antagonist	Anticonvulsant agent
298	Discontinued	Cephalon Inc; Chiron	mecasermin	Diabetic neuropathy; Motor neurone disease; Neurodegenerative disease	Insulin-like growth factor 1 agonist	Neuroprotectant
299	Phase 1 Clinical	Bayer AG / Memory Pharmaceuticals Corp	MEM-1003	Dementia; Alzheimers Disease; Cognitive disorder	Calcium channel modulator	Neuroprotectant
300	*Launched (Phase 3 Clinical)	Merz/Forrest	Memantine	Neurodegenerative disease	NMDA receptor antagonist	Nueroprotectant; Analgesic

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
301	Discontinued	Pharmed Dr Liedike GmbH	Mepindolol	Neurodegenerative disease	Beta adrenoceptor antagonist	Antihypertensive
302	**Discovery	Prescient NeuroPharma Inc	mesencephalic astrocyte-derived neurotrophic factor. Prescient	Parkinsons disease	Neuronal growth factor receptor agonist	Neuroprotectant: Antiparkinsonian
303	**Discovery	Eli Lilly & Co	metabotropic glutamate receptor agonists. Lilly	Pain; Neurodegenerative disease; Anxiety disorder	Metabotropic glutamate receptor 2 agonist; Metabotropic glutamate receptor 3 agonist	Anxiolytic; Analgesic
304	**Discovery	Taisho Pharmaceutical Co Ltd	metabotropic glutamate receptor ligands. Taisho/Merck	Psychosis; Schizophrenia; Major depressive disorder	Metabotropic glutamate receptor agonist; Metabotropic glutamate receptor antagonist	Antipsychotic
305	Discovery	Pharmacyclics Inc	Metallo-tetraphyrins	Neurodegenerative disease; Motor neurone disease: ALS	Chelating agent	Neuroprotectant
306	Discovery	Sibia Neuroscience: Novartis AG	methylphenyle thynylpyridine (MPEP)	Epilepsy; Pain; Neurodegenerative disease; Anxiety disorder; Cerebrovascular ischemia; Head injury	Metabotropic glutamate receptor 5 antagonist; NMDA receptor antagonist; AMPA receptor antagonist	Neuroprotectant; Analgesic; Anticonvulsant agent
307	**Discovery	Prescient NeuroPharma Inc	mGluR agonists, Prescient	Neurodegenerative disease; Anxiety disorder; Ischemia	Metabotropic glutamate receptor agonist	Neuroprotectant; Anxiolytic
308	**Discovery	F Hoffmann-La Roche Ltd	mGluR1 modulator, Roche	Alzheimers disease; Central nervous system disease; Dementia	Metabotropic glutamate receptor 1 modulator	
309	Discovery	Mera Pharmaceuticals Inc	microalgal compound, Astaxanthin	Age related macular degeneration; Hypercholesterolemia; Neurodegenerative disease: Cancer	Antioxidant	Anticancer, Antihypercholesterolemic agent
310	Discontinued	GD Searle & Co	milacemide	Epilepsy; Alzheimers disease; Neurodegenerative disease: Dementia; Depression	MAO B inhibitor; NMDA receptor agonist; Oxidoreductase inhibitor	Antidepressant; Anticonvulsant agent
311	*Launched (Phase 3 Clinical)	Pharmacia/Boehringer	Mirapex (pramipexole);	Alzheimers disease	prevention of autooxidation of dopamine	Neuroprotectant
312	**Phase I Clinical	MitoKor	MITO-4509	Alzheimers disease; Retinitis pigmentosa; Parkinsons disease; Cognitive disorder; Ataxia	Estrogen agonist	Antiparkinsonian
313	**Discovery	MitoKor	MITO-4565	Glaucoma	Apoptosis inhibitor	Neuroprotectant

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
314	**Phase 2 Clinical	Mitsubishi-Tokyo Pharmaceuticals Inc	MKC-231	Alzheimers disease: Amnesia: Cerebrovascular ischemia	Choline uptake enhancer	Neuroprotectant: Nootropic agent
315	**Discovery	Cephalon Inc	MLK inhibitors. Cephalon	Neurodegenerative disease	Protein kinase inhibitor	Neuroprotectant
316	Discontinued	PAION GmbH	MLN-519	Nervous System Inflammation	Proteasome inhibitor	Neuroprotectant: Anti-inflammatory
317	**Phase 2 Clinical	Mochida Pharmaceutical Co Ltd	MND-21, icosapentanoic acid	Alzheimers disease	Platelet aggression antagonist	Neuroprotectant: Antithrombotic
318	No Development Reported	Mitsui Pharmaceuticals Inc	MS-153	Cerebrovascular ischemia	Glutamate receptor modulator	Neuroprotectant
319	No Development Reported	Taisho Pharmaceutical Co Ltd	MT-5	Neurodegenerative disease	Neuronal growth factor receptor agonist	Neuroprotectant
320	No Development Reported	Nisshin Flour Milling Co Ltd	N-3393	Neurodegenerative disease: Cerebrovascular ischemia	No-agonist	Vasodilatory agent
321	**Discovery	Sumitomo Pharmaceuticals Co Ltd	Na ⁺ /H ⁺ exchange inhibitors. Sumitomo	Reperfusion injury; Angina; Cerebrovascular ischemia	H ⁺ K ⁺ ATPase inhibitor, Na ⁺ H ⁺ ion exchange inhibitor	Neuroprotectant: Cardioprotectant; Vasoprotectant; Vasodilatory agent
322	Discovery	Toray Industries Inc	Naltrindole derivatives	Neurodegenerative disease	Delta opioid antagonist	Neuroprotectant
323	Discovery	National Institutes of Health	NAPVSIPO	Neurodegenerative disease	Antioxidant agent	Neuroprotectant
324	*Clinical (Discovery)	Neurocrine Biosciences Inc	NBI-30702	Cerebrovascular ischemia	ACTH releasing factor antagonist	Neuroprotectant
325	Phase 2 Clinical	Neurochem Inc	NC-531	Alzheimers disease	Amyloid protein deposition inhibitor	Neuroprotectant
326	**Phase 2 Clinical	Taisho Pharmaceutical Co Ltd	NE-100	Psychosis; Schizophrenia	Sigma opioid antagonist	Antipsychotic
327	Phase 2 - 3 Clinical	Neotherapeutics	Neotrofin	Neurodegenerative disease	Immunomodulator	Neuroregeneration
328	Phase 2 Clinical	Merz & Co GmbH	Neramexane	Central nervous system disease		Neuroprotectant: Analgesic; Antiparkinsonian
329	Phase 1 Clinical	Tuszynski Lab, UCSD	Nerve growth factor gene therapy	18-month trial to determine whether therapy prevents cell loss in AD. Involves surgical implant.	Nerve growth factor gene therapy	Neuroprotectant
330	Discovery	NsGene A/S	Neublastin	Neurodegenerative disease	Neuronal growth factor	Neuroprotectant

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
331	**Discovery	NeuroSpheres Ltd	neural stem cells. NeuroSpheres	Alzheimers disease; Huntingtons chorea; Motor neurone disease; Multiple sclerosis; Neurodegenerative disease; Parkinsons disease; Schizophrenia; Central nervous system disease; Cerebrovascular ischemia	Tissue regeneration from stem cells	Antipsychotic; Antiparkinsonian
332	**Discovery	Harvard University/ Acorda	neuregulin-2. Acorda	Heart disease; Neurological disease	ErbB2 tyrosine kinase receptor modulator; ErbB3 tyrosine kinase receptor modulator; ErbB4 tyrosine kinase receptor modulator; Unspecified growth factor agonist	Neuroprotectant; Cardioprotectant
333	Discontinued	Apollo Biopharmaceutics Inc	Neurocalc	Alzheimers disease; Neurodegenerative disease	Calcium metabolism modulator	Neuroprotectant
334	**Discovery	Johns Hopkins University	neuroimmunophilin ligands, Guilford	Diabetic neuropathy; Alzheimers disease; Multiple sclerosis; Neurodegenerative disease; Parkinsons disease; Cerebrovascular disease; Cerebrovascular ischemia; Neuropathy	Immunophilin modulator	Chemoprotectant; Neuroprotectant; Antiparkinsonian
335	**Discovery	Acorda Therapeutics Inc	neuronal stem cell therapy. Acorda	Spinal cord injury; Parkinsons disease	Genetically engineered autologous cell therapy; regeneration from stem cells	Antiparkinsonian
336	**Discovery	Vertex Pharmaceuticals Inc	neurophilins (neurological disease). Vertex/ Schering	Alzheimers disease; Multiple sclerosis; Parkinsons disease; Arthritis; Psoriasis; Autoimmune disease; Neurological disease; Diabetes mellitus	General pump inhibitors; P-glycoprotein inhibitor	Antiparkinsonian; Immunosuppressant
337	**Discovery	Renovis Inc	neuroprotectants (nitroene-based). Renovis	Cerebrovascular ischemia; Neurological disease; Injury	Antioxidants	Neuroprotectant
338	**Discovery	Panacea Pharmaceuticals Inc	neuroprotective antioxidants (Alzheimers disease). Panacea	Alzheimers disease; Ischemia	Antioxidants	Neuroprotectant; Antioxidant agent

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
339	No Development Reported	Neurocal International Inc	Neurostrol	Alzheimers disease; Neurodegenerative disease	Antioxidants	Neuroprotectant
340	**Discovery	BioVex Ltd	NeuroVEX	Spinal cord injury; Pain; Neurodegenerative disease; Parkinsons disease	Dopamine synthesis stimulant; Herpes virus based gene therapy; Dopamine modulator	Antiparkinsonian
341	**Discovery	Institut Henri Beaufour	nitric oxide synthase inhibitors. Institut Henri Beaufour	Neurodegenerative disease; Cerebrovascular ischemia	NO synthesis inhibitor	Neuroprotectant; Free radical scavenger
342	Discontinued	AstraZeneca plc	NLA-715; Clomethiazole; Zendra	Epilepsy; Cerebrovascular ischemia. Parkinsons disease. Epilepsy. Alzheimers disease	GABA A agonist	Neuroprotectant. Anticonvulsant agent
343	**Discovery	Hoffmann-La Roche AG	NMDA antagonists. Roche	Neurodegenerative disease; Central nervous system disease; Cerebrovascular ischemia	NMDA receptor antagonist	Neuroprotectant
344	**Discovery	Hokkaido University	NMDA antagonists. Hokkaido University/Asahi Kasei	Neurodegenerative disease	NMDA receptor antagonist	Neuroprotectant
345	**Discovery	Sumitomo Pharmaceuticals Co Ltd	NMDA antagonists, Sumitomo	Epilepsy; Neurodegenerative disease; Cerebrovascular ischemia	NMDA/Glycine antagonist; NMDA receptor antagonist	Neuroprotectant; Anticonvulsant agent
346	**Phase I Clinical	Pfizer Inc	NMDA/glycine antagonists, Pfizer	Cerebrovascular ischemia	NMDA/Glycine antagonist	Neuroprotectant
347	**Discovery	Merz & Co GmbH	NMDA glycine site antagonists. Merz	Epilepsy; Pain; Neurodegenerative disease; Cerebrovascular ischemia	NMDA/Glycine antagonist	Neuroprotectant; Analgesic; Anticonvulsant agent
348	**Discovery	Merck Sharp & Dohme Research Laboratories	NMDA receptor antagonists (NR2B subtype-selective). Merck & Co	Epilepsy; Neuropathic pain; Parkinsons disease; Cerebrovascular ischemia	NMDA receptor antagonist	Neuroprotectant; Analgesic; Antiparkinsonian; Anticonvulsant agent
349	No Development Reported	Novo Nordisk A/S	NNC-07-0775	Cerebrovascular ischemia.; Epilepsy	Metabotropic glutamate receptor 1 antagonist. Ionotropic glutamate receptor antagonist	Neuroprotectant
350	Discontinued	Novo Nordisk A/S	NNC-07-9202	Epilepsy; Neurodegenerative disease; Psychosis; Cerebrovascular ischemia	Neuroprotectant; NMDA receptor antagonist; Ampa receptor antagonist	Neuroprotectant; Antipsychotic; Anticonvulsant agent

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
351	No Development Reported	Regeneron Pharmaceuticals Inc	Noggin	Neurodegenerative disease	Growth factor agonist	Neuroprotectant
352	**Discovery	Biogen Inc	Nogo receptor modulators. Biogen Idec	Spinal cord injury; Multiple sclerosis; Cerebrovascular ischemia; Brain injury	Neuronal growth factor receptor modulator	Neuroprotectant
353	**Discovery	Organix Inc	nonamines. Organix	Parkinsons disease; Central nervous system disease; Cocaine addiction	Monoamine uptake inhibitor	Antiparkinsonian
354	No Development Reported	Hedral Therapeutics Inc	Norleu	Neurodegenerative disease; Cerebrovascular ischemia	angiokine	Vasodilatory agent
355	Phase 1 Clinical	Medinox Inc	NOX-700	Neurodegenerative disease	NO modulator	Antioxidant agent
356	Discovery	NPS Pharmaceuticals Inc	NPS-1407	Epilepsy; Pain; Neurodegenerative disease; Cerebrovascular ischemia; Depression	NMDA receptor antagonist	Antidepressant; Analgesic; Anticonvulsant agent
357	Discontinued	NPS Pharmaceuticals Inc	NPS-846	Epilepsy; Pain; Neurodegenerative disease; Cerebrovascular ischemia	Ionotropic glutamate receptor antagonist	Neuroprotectant; Anticonvulsant agent
358	Discovery	Centaur Pharmaceuticals Inc	NRT-115	Multiple sclerosis, Inflammation	Cytokine release modulator	Anti-inflammatory
359	Discontinued	NeuroSearch AS	NS-1209	Neurodegenerative disease; Cerebrovascular ischemia	AMPA receptor antagonist	Neuroprotectant
360	Research Tool	NeuroSearch AS	NS-1608	Cerebrovascular ischemia	Potassium channel activator	Neuroprotectant
361	Phase 2 Clinical	NeuroSearch	NS-2330	Neurodegenerative disease; Parkinsons disease	Dopamine reuptake inhibitor	Neuroprotectant
362	Discontinued	NeuroSearch AS	NS-257	Neurodegenerative disease; Cerebrovascular ischemia	AMPA receptor antagonist	Neuroprotectant
363	Discontinued	NeuroSearch AS	NS-377	Alzheimers disease; Neurodegenerative disease; Cognitive disorder	AMPA receptor antagonist	Neuroprotectant
364	Discontinued	NeuroSearch AS	NS-638	Neurodegenerative disease; Cerebrovascular ischemia	Calcium channel blocker	Neuroprotectant; Vasodilatory agent

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
365	Discontinued	NeuroSearch AS	NS-649	Alzheimers disease: Neurodegenerative disease: Cognitive disorder	Calcium channel blocker	Neuroprotectant
366	**Discovery	Genentech Inc/ Ceregene	NT-4/5, Genentech	Age related macular degeneration: Glaucoma: Huntingtons chorea: Motor neurone disease: Parkinsons disease: Uveitis: Diabetic retinopathy: Neurological disease: Hearing disorder	Neurotrophin-4/5 agonist	Neuroprotectant: Antiparkinsonian
367	**Discovery	Newron Pharmaceuticals SpA	NW-1048	Epilepsy: Parkinsons disease	MAO B inhibitor	Antiparkinsonian
368	Discovery	Nymox Pharmaceutical Corp	NXD-5150	Neurodegenerative disease	Unidentified	Neuroprotectant
369	**Discovery	Nymox Pharmaceutical Corp	NXD-9062	Alzheimers disease	Spheron conversion inhibitor	Neuroprotectant
370	Phase 3 Clinical	Centaur Pharmaceuticals Inc. Astra Zeneca plc	NXY-059	Alzheimers disease: Multiple sclerosis: Neurodegenerative disease: Arthritis: Cerebrovascular ischemia	Free radical scavenger: NO synthesis inhibitor	Neuroprotectant
371	**Phase 2 Clinical	Janssen Pharmaceutica NV	ocaperidone	Schizophrenia	Dopamine D2 antagonist; 5-HT 2a antagonist	Antipsychotic
372	Discontinued	Novo Nordisk A/S	odapipam	Neurodegenerative disease: Psychosis: Schizophrenia	Dopamine D1 antagonist	Antipsychotic
373	*Launched (Phase 2 Clinical)	Lilly	Olanzapine	Alzheimers disease	5-HT2 receptor antagonist: Dopamine D2 receptor antagonist	Antipsychotic
374	*Phase 2 Clinical (Phase 1 Clinical)	Ono Pharmaceutical Co Ltd	ONO-2506	Cerebrovascular Ischemia, Parkinsons Disease		Neuroprotectant; Antiparkinsonian
375	No Development Reported	Otsuka Pharmaceuticals Co Ltd	OPC-14117	Dementia, Cerebrovascular ischemia, Dementia, Huntingtons chorea	Free radical scavenger	Neuroprotectant; Antiparkinsonian
376	**Phase 2 Clinical	Cortex Pharmaceuticals Inc	Org-24448	Schizophrenia: Major depressive disorder	AMPA receptor modulator	Antidepressant; Antipsychotic
377	**Phase 2 Clinical	Sanofi-Synthelabo	osanetant	Phlebothrombosis: Pain: Schizophrenia: Deep vein thrombosis: Major depressive disorder	NK agonist: NK3 antagonist	Anxiolytic; Antipsychotic; Antidepressant
378	**Discovery	Serono SA	osteopontin, Serono	Multiple sclerosis	NOS inhibitor: Cytokine	Neuroprotectant

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
379	**Discovery	National Institutes of Health	p53 inhibitors (neurodegenerative disease). NIH	Neurodegenerative disease: Toxicity	Apoptosis inhibitor	Neuroprotectant
380	Phase 2 Clinical	Phytopharm plc	P-58	Dementia; Alzheimers disease; Parkinsons disease	Muscarinic M1 modulator	Neuroprotectant; Nootropic agent
381	No Development Reported	Aventis	P-9939	Neurodegenerative disease	Glycine partial agonist	
382	Phase 1 Clinical	Tulane University	PACAP	Neurodegenerative disease; Cerebrovascular ischemia	Pituitary adenylate cyclase activating polypeptide (PACAP); Adenylate cyclase stimulator	Neuroprotectant
383	**Phase 3 Clinical	Johnson & Johnson	paliperidone	Schizophrenia	5-HT antagonist	Antipsychotic
384	Phase 3 Clinical	Lifegroup SpA	palmidrol	Neurodegenerative disease; Inflammation	5-HT release inhibitor	Neuroprotectant; Anti-inflammatory
385	Discovery	Panacea Pharmaceuticals Inc	PAN-811	Alzheimers disease	Antioxidant agent	Neuroprotectant
386	No Development Reported	Regeneron Pharmaceuticals Inc	Pan-Neurotrophin-1	Alzheimers disease; Neurodegenerative disease; Psychosis	Unspecified growth factor agonist	Neuroprotectant; Antipsychotic
387	**Discovery	CellFactors plc	Parkinsons disease cell therapy, Cell Factors	Parkinsons disease	Cell therapy	Antiparkinsonian
388	**Discovery	Boston Life Sciences Inc	Parkinsons disease therapeutics, Boston Life Sciences	Parkinsons disease; Attention deficit hyperactivity disorder	Dopamine uptake inhibitor	Antiparkinsonian
389	**Discovery	Panacea Pharmaceuticals Inc	Parkinsons therapeutic peptides, Panacea	Parkinsons disease	Antiparkinsonian	
390	**Discovery	Johns Hopkins University	PARP inhibitors, Guilford	Diabetic neuropathy; Spinal cord injury; Alzheimers disease; Myocardial infarction; Neurodegenerative disease; Parkinsons disease; Cerebrovascular ischemia; Cancer; Head injury; Septic shock	PARP inhibitor	Radiosensitizer; Neuroprotectant; Antiparkinsonian
391	**Discovery	Cephalon Inc.	PARP-1 inhibitor, Cephalon	Cerebrovascular ischemia; Cancer	PARP inhibitor	Anticancer, Neuroprotectant
392	**Discovery	Fujisawa Pharmaceutical Co Ltd	PARP-1 inhibitors, Fujisawa	Parkinsons disease	PARP inhibitor	

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
393	**Discovery	Sumitomo Pharmaceuticals Co Ltd	PARP-1 inhibitors (stroke). Sumitomo	Cerebrovascular ischemia	PARP inhibitor	Neuroprotectant
394	**Discovery	University of Florence	PARP-1 inhibitors. University of Florence/ GlaxoSmithKline	Cerebrovascular ischemia	PARP inhibitor	Neuroprotectant
395	Phase 2 Clinical	Prana Biotechnology	PBT-1: Clioquinol	Alzheimers disease	Chelating agent: Beta amyloid modulator	Neuroprotectant
396	No Development Reported	Parke-Davis & Co	PD-132026	Neurodegenerative disease	Dopamine agonist	Neuroprotectant: Antipsychotic
397	**Discovery	Parke-Davis & Co	PD-148903	Parkinsons disease	Dopamine D1 agonist: Dopamine D2 agonist	Antiparkinsonian
398	No Development Reported	Pfizer Inc	PD-150606	Neurodegenerative disease: Neuropathy	Calpain inhibitor	Neuroprotectant
399	Discovery	Pfizer Inc	PD-159265	Neurodegenerative disease	AMPA receptor antagonist	Neuroprotectant
400	No Development Reported	Parke-Davis & Co	PD-90780	Nervous system tumor: Neurodegenerative disease	NGF antagonist	Neuroprotectant
401	No Development Reported	Pharmaceutical Discovery Corp	PDC-008.004	Alzheimers disease; Neurodegenerative disease	Muscarinic M2 agonist	Nootropic agent
402	**Discovery	Memory Pharmaceuticals Corp	PDE-4 inhibitors, Memory	Alzheimers disease; Parkinsons disease; Schizophrenia; Cognitive disorder; Major depressive disorder	PDE 4 inhibitor	Nootropic agent; Antidepressant; Antipsychotic; Antiparkinsonian
403	Discovery	INSERM	PE21	Neurodegenerative disease; Parkinsons disease	Dopamine uptake inhibitor	Antiparkinsonian
404	**Phase 2 Clinical	Wyeth Research	perzinfotel	Pain; Cerebrovascular ischemia; Neuropathy	NMDA receptor antagonist	Neuroprotectant: Analgesic
405	**Discovery	Alexion Pharmaceuticals Inc	pexelizumab	Myocardial infarction: Angina: Cardiovascular inflammation: Cerebrovascular ischemia	Complement cascade inhibitor	Cardioprotectant: Vasoprotectant
406	*Phase 3 Clinical (Discovery)	Axonyx Inc/NIH	Phenserine:	Alzheimers disease	Acetylcholinesterase inhibitor	Anti-amyloidogenic
407	Discovery	University of Nottingham	Philanthotoxins	Neurodegenerative disease: Cognitive disorder	Nicotinic ACh antagonist: AMPA receptor antagonist	Nootropic agent

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
408	*No Development Reported (Discovery)	Pierre Fabre SA	Piperidine derivatives	Alzheimers disease; Neurodegenerative disease; Parkinsons disease	Alpha 1 adrenoceptor antagonist; Alpha 2 adrenoceptor antagonist	Antiparkinsonian
409	Discovery	Universita di Siena	PK-11195 analogs	Neurodegenerative disease; Anxiety disorder	Dopamine D2 antagonist; 5-HT 1a antagonist; Glutamate release inhibitor	Anxiolytic; Imaging agent; BDZ agonist
410	Discovery	Proneuron Biotechnologies Inc	PN-277	Neurodegenerative disease		Neuroprotectant; Immunomodulator
411	**Discovery	Wellstat Therapeutics Corp	PN-401	Leukopenia, drug induced; Stomach tumor; Gastrointestinal tumor; Neurodegenerative disease; Pancreas tumor; Colorectal tumor	Uracil metabolism modulator	Anticancer; Neuroprotectant
412	Discontinued	Pharmacia & Upjohn Inc	PNU-87663	Neurodegenerative disease	Coagulation inhibitor; Antithrombin III	Antioxidant agent
413	**Research Tool	Pharmacia & Upjohn Inc	PNU-99194A	Schizophrenia	Dopamine D3 antagonist	Antipsychotic
414	No Development Reported	Pharmacia & Upjohn Inc	PNU-101033E	Neurodegenerative disease; Ischemia		Neuroprotectant; Antioxidant agent
415	No Development Reported	Pharmacia & Upjohn Inc	PNU-157678	Neurodegenerative disease	Unclassified enzyme inhibitor	Neuroprotectant
416	**Phase 2 Clinical	Pharmacia Corp	PNU-170413	Psychosis; Schizophrenia	Dopamine D3 antagonist	Antipsychotic
417	**Phase 1 Clinical	Pharmacia Corp	PNU-177864	Schizophrenia	Dopamine D3 antagonist	Antipsychotic
418	*Clinical (Discovery)	Polifarma SpA	POL-255	Diabetic neuropathy; Neurodegenerative disease; Schizophrenia	Dopamine agonist	Antipsychotic
419	**Discovery	University of Kuopio	POP inhibitor (Alzheimers). Finncover/ University of Kuopio	Alzheimers disease	Prolylendopeptidase inhibitor	Neuroprotectant
420	Discontinued	Gedeon Richter Ltd	posatirelin	Neurodegenerative disease	TRH agonist	Neuroprotectant
421	**Discovery	Bristol-Myers Squibb Co	potassium channel modulators. BMS	Cerebrovascular ischemia	Potassium channel modulator	Neuroprotectant
422	No Development Reported	Praecis Pharmaceuticals Inc	PPI-368	Alzheimers disease; Neurodegenerative disease	Amyloid protein deposition inhibitor	Neuroprotectant
423	Discovery	Prescient NeuroPharma Inc	PRE-103	Neurodegenerative disease; Anxiety disorder; Ischemia	Metabotropic glutamate receptor agonist	Neuroprotectant; Anxiolytic

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
424	Discontinued	Takeda Chemical Industries Ltd	Protirelin	Alzheimers disease: Neurodegenerative disease: Dementia	TRH agonist	Nootropic agent
425	Discovery	Pharmos Corp	PRS-211220	Multiple sclerosis: Neurodegenerative disease: Parkinsons disease: Cerebrovascular ischemia: Nervous system inflammation: Brain injury	Cyclooxygenase 2 inhibitor: Chemokine antagonist: NMDA receptor antagonist: Cannabinoid agonist: Cytokine modulator	Neuroprotectant: Analgesic: Antiparkinsonian: Non-steroidal anti-inflammatory
426	**Discovery	ProteoTech Inc	PTI-777	Amyloidosis: Alzheimers disease: Parkinsons disease: Non-insulin dependent diabetes	Amyloid protein deposition inhibitor	Neuroprotectant
427	**Phase 1 Clinical	Phytopharm plc	PYM-50018	Motor neurone disease: Neuromuscular disease: Cardiac failure	β -adrenoceptor antagonist	Neuroprotectant: Cardioprotectant
428	Phase 2 Clinical	Phytopharm plc	PYM-50028	Alzheimers disease: Neurodegenerative disease: Parkinsons disease	Dopamine modulator	Neuroprotectant: Nootropic agent
429	**Discovery	Ferrer Internacional SA	pyrimidin-5-one	Schizophrenia		Antipsychotic
430	Discovery	Quark Biotech Inc	QG-2283	Neurodegenerative disease	Hypoxia protection	Neuroprotectant
431	**Phase 2 Clinical	Quigley Pharma Inc	QR-333	Diabetic neuropathy	Carbohydrate metabolism modulator	Neuroprotectant
432	**Phase 1 Clinical	Roche Holding AG	R-1485	Alzheimers disease	Unspecified GPCR modulator	Neuroprotectant
433	**Discovery	Roche Holding AG	R-1577	Alzheimers disease	Unclassified enzyme inhibitor	Neuroprotectant
434	**Discovery	Roche Holding AG		Alzheimers disease	Unspecified GPCR modulator	Neuroprotectant
435	*Pre-registration (Phase 3 Clinical)	Teva Pharmaceutical Industries Ltd	Rasagiline	Alzheimers disease: Neurodegenerative disease: Parkinsons disease	Apoptosis inhibitor: MAO B inhibitor	Antiparkinsonian
436	Discontinued	Centaur Pharmaceuticals Inc	REN-1654	Alzheimers disease: Multiple sclerosis	Anti-inflammatory	Neuroprotectant: Antiparkinsonian
437	Discovery	ReNeuron (UK) Ltd	ReN-1820	Alzheimers disease: Inflammation: Pain: Neurodegenerative disease: Dementia	NGF antagonist	Nootropic agent: Analgesic: Anti-inflammatory
438	**Phase 2 Clinical	Bayer AG	repinotan	Cerebrovascular ischemia: Brain injury: Major depressive disorder	5-HT 1a agonist	Neuroprotectant: Antidepressant

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
439	**Phase 2 Clinical	ASTA Medica AG	retigabine	Epilepsy	GABA A agonist; Potassium channel activator; Vasodilatory agent; Anticonvulsant agent	
440	**Phase 3 Clinical	RepliGen Corp	RG-1068	Anxiety disorder; Pancreatitis; Schizophrenia; Autism; Obsessive-compulsive disorder	Secretin agonist	
441	Discovery	Rinat Neuroscience Corp	RI-820	Motor neurone disease; Spinal muscular atrophy	Protein based therapeutic	Neuroprotectant
442	*Launched (Phase 3 Clinical)	Aventis	Rilutek (Riluzole) + Dopamine Agonist;	Parkinsons disease	Protein kinase C inhibitor; Sodium channel blocker; glutamate release inhibitor	Neuroprotectant
443	**Launched	Alkermes Inc	risperidone (controlled release; Medisorb). Alkermes/Janssen	Schizophrenia	5-HT 2 antagonist; Dopamine D2 antagonist; Antipsychotic	
444	**Phase 3 Clinical	Aderis Pharmaceuticals Inc	rotigotine	Restless legs syndrome; Parkinsons disease	Dopamine D3 agonist	
445	No Development Reported	R J Reynolds Tobacco Co	RJR-1401	Alzheimers disease; Neurodegenerative disease	Nicotinic ACh agonist	Nootropic agent
446	**Discovery	R J Reynolds Tobacco Co	RJR-2429	Alzheimers disease; Parkinsons disease; Dementia	Nicotinic ACh agonist	Nootropic agent; Antiparkinsonian
447	No Development Reported	Roche	Ro-09-2210	Neurodegenerative disease; Autoimmune disease	MAP kinase inhibitor	Immunomodulator
448	Discontinued	Schering AG	Rolipram	HIV infection; Multiple sclerosis; Neurodegenerative disease; Asthma; Tardive dyskinesia; Depression	PDE 4 inhibitor; TNF antagonist	Nootropic agent; Antidepressant
449	**Phase 3 Clinical	SmithKline Beecham plc	ropinirole (controlled release; GEOMATRIX). GlaxoSmithKline	Parkinsons disease	Dopamine D2 agonist; Dopamine D3 agonist	Antiparkinsonian
450	No Development Reported	Rhone-Poulenc Rorer Inc	RPR-104632	Neurodegenerative disease	NMDA receptor antagonist	Neuroprotectant
451	Discovery	Roche	RS-100642	Neurodegenerative disease; Cerebrovascular ischemia	Sodium channel blocker	Neuroprotectant

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
452	Discontinued	Shionogi & Co Ltd	S-312-d	Neurodegenerative disease; Cerebrovascular ischemia	Calcium channel blocker	Antihypertensive; Class IV antiarrhythmic agent
453	**Phase 1 Clinical	Shionogi & Co Ltd	S-1746	Cerebrovascular ischemia; Head injury	NMDA receptor modulator; AMPA receptor antagonist	Neuroprotectant
454	**Discovery	Servier	S-14297	Psychosis; Schizophrenia	Dopamine D3 antagonist; 5-HT 2a antagonist	Antipsychotic
455	No Development Reported	Servier	S-14820	Neurodegenerative disease; Central nervous system disease	TRH agonist	Neuroprotectant
456	Discovery	Servier	S-176251; S-34730-1; S-34730	Neurodegenerative disease; Cerebrovascular ischemia; Seizure; epilepsy & convulsion	AMPA receptor antagonist	Neuroprotectant; Anticonvulsant agent
457	*Phase 1 Clinical (Discovery)	Servier	S-18986	Neurodegenerative disease; Cognitive disorder; Cerebrovascular ischemia	Glutamate receptor antagonist; AMPA receptor modulator	Neuroprotectant
458	Discovery	Servier	S-33113-1	Neurodegenerative disease; Cerebrovascular ischemia	Antioxidant agent	Neuroprotectant
459	**Discovery	Servier	S-33138	Psychosis; Schizophrenia	Dopamine D3 antagonist	Antipsychotic
460	Discontinued	Janssen Pharmaceutica	sabeluzole	Alzheimers disease; Dementia	Hypoxia protection	Neuroprotectant
461	Phase 2 Clinical	Newron Pharmaceuticals SpA	Safnamide	Parkinsons disease; Epilepsy	Calcium channel blocker; Dopamine uptake inhibitor	Neuroprotectant; Antiparkinsonian
462	**Phase 2 Clinical	Merck KGaA	sarizotan	Parkinsons disease; Psychosis; Schizophrenia; Tardive dyskinesia	Dopamine antagonist; Dopamine D2 antagonist; 5-HT 1a agonist	Antipsychotic; Antiparkinsonian
463	**Research Tool	SmithKline Beecham plc	SB-203580	Alzheimers disease; Inflammation; Rheumatoid arthritis; Asthma; Ischemia; Cerebrovascular ischemia; Vascular disease	Cytokine release inhibitor; p38 MAP kinase inhibitor; Anti-inflammatory	Neuroprotectant; Vasoprotectant
464	Discontinued	GlaxoSmithKline plc	SB-271046	Alzheimers disease; Schizophrenia	5-HT antagonist	Antipsychotic
465	Discovery	GlaxoSmithKline plc	SB-277011	Schizophrenia	Dopamine D3 antagonist	Antipsychotic

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
466	**Phase 1 Clinical	Wyeth	SCA-136	Schizophrenia	5-HT modulator	Psychomodulator
467	**Research Tool	Schering-Plough Corp	Sch-58261	Neurodegenerative disease: Parkinsons disease; Neurological disease	Adenosine A2a antagonist	
468	**Discovery	Taisho Pharmaceutical Co Ltd	SEA-0400	Cerebrovascular ischemia	Na+ Ca2+ ion exchange inhibitor	Neuroprotectant
469	Phase 2 Clinical	Russian Academy of Sciences	SEMAX	Alzheimers disease; Neurodegenerative disease; Cerebrovascular ischemia	ACTH agonist	Neuroprotectant; Vasoprotectant
470	**Discovery	Guilford Pharmaceuticals Inc	serine racemase inhibitors, Guilford	Neurodegenerative disease	Unclassified enzyme inhibitor; Glutamate release inhibitor	Neuroprotectant
471	Discovery	SIBIA Neurosciences Inc	SIB-1553A	Neurological disease; Parkinsons disease	Nicotinic ACh modulator	Antiparkinsonian
472	Phase 2 Clinical	SIBIA Neurosciences Inc	SIB-1553A	Alzheimers disease	Nicotinic ACh modulator	Antiparkinsonian
473	No Development Reported	SIBIA Neurosciences Inc	SIB-1765F	Alzheimers disease	Nicotinic ACh agonist	Nootropic agent; Antiparkinsonian
474	Discovery	Schering-Plough Corp	Siclofen	Neurodegenerative disease	GABA B agonist	Neuroprotectant
475	**Discovery	Eli Lilly & Co	SGS-518	Schizophrenia; Cognitive disorder	5-HT 6 antagonist;	Nootropic agent
476	Discovery	Senju Pharmaceutical Co Ltd	SJA-6017	Muscular dystrophy; Neurodegenerative disease; Cataract; Cerebrovascular ischemia	Cysteine protease inhibitor; Calpain inhibitor	Neuroprotectant
477	**Research Tool	SmithKline Beecham plc	SKF-38393	Parkinsons disease; Non-insulin dependent diabetes	Dopamine D1 agonist; Insulin receptor modulator	Antiparkinsonian; Hypoglycemic agent; Antihypercholesterolemic agent
478	No Development Reported	GlaxoSmithKline plc	SKF-74652	Alzheimers disease; Neurodegenerative disease	Beta amyloid generation inhibitor; Amyloid protein deposition inhibitor	Anti-amyloidogenic
479	**Discovery	SmithKline Beecham plc	SKF-82958	Parkinsons disease	Dopamine D1 agonist	Antiparkinsonian
480	No Development Reported	Synthelabo	SL-34.0026	Neurodegenerative disease; Parkinsons disease	MAO B inhibitor	Antiparkinsonian
481	**Phase 2 Clinical	Sanofi-Synthelabo	SL-65.0155	Alzheimers disease	5-HT 4 antagonist; 5-HT 4 agonist	Neuroprotectant; Nootropic agent
482	Discontinued	Solvay SA	SLV-308	Parkinsons disease	Dopamine D2 agonist; Adrenoceptor agonist; 5-HT 1a agonist	Neuroprotectant; Antiparkinsonian

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
483	**Phase 1 Clinical	Solvay SA	SLV-314	Psychosis: Schizophrenia	5-HT 1a receptor modulator; Dopamine D2 antagonist; 5-HT uptake inhibitor	Antipsychotic
484	**Phase 1 Clinical	Solvay SA	SLV-319	Obesity; Psychosis: Schizophrenia; Metabolic disorder	Dopamine D2 antagonist; Cannabinoid CB1 antagonist; 5-HT 1a agonist	Antipsychotic
485	**Phase 2 Clinical	Sumitomo Pharmaceuticals Co Ltd	SM-13496	Schizophrenia	5-HT 2 antagonist; Dopamine D2 antagonist	Antipsychotic
486	No Development Reported	Elan Pharmaceuticals Inc	SNX-482	Neurodegenerative disease	Calcium channel blocker	Nootropic agent
487	Discovery	Supratek Pharma Inc	SP-(V5.2)C	Neurodegenerative disease	VEGF antagonist	Anticancer; Antiarrhythmic agent
488	Discovery	Celgene Corp	SPC-9766	Neurodegenerative disease; Parkinsons disease; Ischemia; Cerebrovascular ischemia	Jun N terminal kinase inhibitor	Neuroprotectant; Antiparkinsonian
489	Discovery	Sanochemia Pharmazeutika AG	SPH-1371	Alzheimers disease; Dementia	Cholinesterase inhibitor	Neuroprotectant
490	**Discovery	Biofrontera Pharmaceuticals GmbH	sphingomyelinase inhibitors, Biofrontera	Neurodegenerative disease	Sphingomyelinase inhibitor	
491	**Discovery	Sagami Chemical Research Center	sphingomyelinase inhibitors, Taisho/Sagami	Neurodegenerative disease; Cerebrovascular ischemia	Sphingomyelinase inhibitor	Neuroprotectant; Nootropic agent
492	Discovery	Alviva Biopharmaceuticals Inc / Schwarz	SPM-914	Alzheimers disease; Huntingtons chorea; Motor neurone disease; Neurodegenerative disease; Parkinsons disease	Apoptosis inhibitor	
493	Discovery	Albert-Ludwigs-Universität Freiburg	SPM-935	Neurodegenerative disease		Neuroprotectant
494	**Phase 2 Clinical	Sanofi-Synthelabo	SR-57667	Alzheimers disease; Parkinsons disease	Growth factor stimulator; anti-apoptotic	Neuroprotectant; Nootropic agent; Antiparkinsonian
495	Phase 2 Clinical	Wyeth	SRA-333	<u>Alzheimers disease</u>	<u>5-HT 1a antagonist</u>	Nootropic agent
496	**Discovery	Purdue Neuroscience Corp	SSNRAs, Purdue Neuroscience/ Pfizer	Ocular disease; Parkinsons disease; Psychosis; Central nervous system disease; Cerebrovascular ischemia; Head injury	NMDA/Glycine antagonist; NMDA receptor antagonist	Neuroprotectant; Antipsychotic; Antiparkinsonian

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
497	**Phase 1 Clinical	Sanofi-Synthelabo	SSR-125047	Schizophrenia	Sigma opioid modulator	Antipsychotic
498	**Phase 1 Clinical	Sanofi-Synthelabo	SSR-146977	Anxiety disorder; Schizophrenia; Major depressive disorder	NK3 antagonist	Antidepressant; Anxiolytic; Antipsychotic
499	Phase 1 Clinical	Sanofi-Synthelabo	SSR-180575	Nervous system injury; Neurodegenerative disease	Benzodiazepine agonist	Neuroprotectant; Nootropic agent
500	**Phase 1 Clinical	Sanofi-Synthelabo	SSR-181507	Schizophrenia	Dopamine D2 antagonist; 5-HT 1a agonist	Antipsychotic
501	Discovery	Sanofi-Synthelabo	SSR-482073	Neurodegenerative disease	Benzodiazepine agonist	Neuroprotectant; Nootropic agent
502	**Discovery	Sanofi-Synthelabo	SSR-504734	Schizophrenia	Glycine modulator	Antipsychotic
503	**Discovery	BresaGen Ltd	stem cell therapy. BresaGen	Spinal cord injury; Parkinsons disease; Thalassemia; Cerebrovascular ischemia	Antiparkinsonian	Neuroprotectant
504	Phase 3 Clinical	Pfizer Inc	Sumanriole	Parkinsons disease	Dopamine D2 agonist	Neuroprotectant; Antiparkinsonian
505	No Development Reported	Suntory Ltd	SUN-CS174	Neurodegenerative disease	5-HT 2 antagonist	Vasodilatory agent
506	**Phase 1 Clinical	Daiichi Suntory Biomedical Research Co Ltd	SUN-N8075	Cerebral infarction	Na+ Ca2+ ion exchange inhibitor; Vasodilatory agent; Sodium channel blocker; Antioxidant agent; Calcium channel blocker	Neuroprotectant
507	No Development Reported	Allelix Neuroscience Inc	survivins	Neurodegenerative disease	Modification of signal transduction of neurotrophic pathways	Neuroprotectant
508	**Discovery	PoliChem SA	sustained release dihydro-ergocryptine. Polichem/ SIRENADE	Alzheimers disease; Migraine; Parkinsons disease	Dopamine agonist	Neuroprotectant
509	Discovery	Annovis Inc	SYM-2207	Alzheimers disease; Neurodegenerative disease; Cerebro-vascular ischemia	AMPA receptor antagonist	Neuroprotectant
510	Phase 2 Clinical	Toyama Chemical Co Ltd	T-588	Alzheimers disease	Protein kinase stimulator; Acetylcholine release stimulator	Neuroprotectant
511	Discontinued	American Biogenetic Sciences Inc	tacrine analogs. ABS-301. ABS-302. ABS-304	Alzheimers disease; Neurodegenerative disease	Acetylcholinesterase inhibitor	Neuroprotectant

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
512	No Development Reported	Eli Lilly & Co/IVAX Corp	talampatel	Cerebrovascular ischemia; Motor neuron disease	AMPA receptor agonist	Neuroprotectant
513	Phase 2 Clinical	IVAX Corp	talampatel	Epilepsy; Parkinsons disease	AMPA receptor agonist	Neuroprotectant
514	**Phase 2 Clinical	SmithKline Beecham plc	talnetant	Chronic obstructive pulmonary disease; Irritable bowel syndrome; Pain; Schizophrenia; Asthma; Micturition disorder; Cough	NK3 antagonist	Antitussive; Antipsychotic; Analgesic
515	*Launched (Phase 3 Clinical)	Tanabe Seiyaku Co Ltd	Taltirelin	Alzheimers disease; Dementia	TRH agonist; Dopamine modulator	TRH agonist
516	Discontinued	Takeda Chemical Industries Ltd	TAN-950A	Neurodegenerative disease	Ionotropic glutamate receptor agonist; NMDA receptor agonist	Neuroprotectant
517	**Phase 2 Clinical	Targacept Inc	TC-1734	Alzheimers disease; Parkinsons disease	Nicotinic ACh modulator	Antiparkinsonian
518	Discovery	Targacept Inc	TC-2559	Neurodegenerative disease	Nicotinic ACh agonist	Nootropic agent
519	Phase 2 Clinical	Novartis AG	TCH-346	Parkinsons disease; Motor neuron disease	Metabotropic glutamate receptor 2 agonist	Neuroprotectant; Nootropic agent; Antiparkinsonian
520	Discontinued	Takeda Chemical Industries Ltd	TGP-580	Neurodegenerative disease; Peptic ulcer; Wound healing	FGF-2 agonist	Neuroprotectant
521	Discovery	Thuris Corp	Thurinex	Alzheimers disease	Amyloid protein deposition inhibitor	Neuroprotectant
522	Discovery	Lonza Group	TK-14	Neurodegenerative disease		Neuroprotectant
523	**Discovery	Digital Gene Technologies Inc	TOGA technology, DGT	Alzheimers disease; Inflammatory bowel disease; Neoplasm; Parkinsons disease; Atherosclerosis; Gastrointestinal inflammation		Anti-arteriosclerotic; Antiparkinsonian
524	Discontinued	AVANT Immunotherapeutics Inc	TP-20	Multiple sclerosis; Neurodegenerative disease	Complement Factor inhibitor; Selectin antagonist	Cardioprotectant; Immuno-suppressant
525	Discovery	Pfizer Inc	traxoprodil	Neurodegenerative disease; Parkinsons disease	NMDA receptor antagonist	Neuroprotectant; Analgesic; Antiparkinsonian
526	Phase 2 Clinical	Pfizer Inc	traxoprodil	Cerebrovascular ischemia	NMDA receptor antagonist	Neuroprotectant; Analgesic; Antiparkinsonian

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
527	**Discovery	Pharmos Corp	tricyclic dextro-cannabinoids. Pharmos	Neuropathic pain: Inflammation: Inflammatory bowel disease: Multiple sclerosis: Neurodegenerative disease: Parkinsons disease: Rheumatoid arthritis: Autoimmune disease: Cerebrovascular ischemia: Nervous system inflammation: Brain injury	Cyclooxygenase 2 inhibitor: Immunomodulator: Chemokine antagonist: NMDA receptor antagonist: Non-steroidal anti-inflammatory: Cannabinoid agonist: Cytokine modulator	Neuroprotectant: Analgesic: Antiparkinsonian
528	**Phase 1 Clinical	Taisho Pharmaceutical Co Ltd	TS-011	Cerebral infarction	Arachidonic acid metabolism inhibitor	Neuroprotectant: Anti-inflammatory
529	No Development Reported	Pharmacia & Upjohn Inc	U-74500A	Neurodegenerative disease	Aminosteroid	Neuroprotectant
530	Discontinued	Pharmacia & Upjohn Co	U-78517F	Alzheimers disease: Inflammation: Neurodegenerative disease: Cerebro-vascular ischemia	Lipid peroxidation inhibitor	Vasoprotectant: Anti-inflammatory: Antioxidant agent
531	**Discovery	Universidad Complutense de Madrid	UCM-3100	Psychiatric disorder, Neurological disease	5-HT 7 receptor modulator	
532	**Research Tool	Astra AB	UH-232	Schizophrenia	Dopamine D3 antagonist: Antipsychotic	
533	Discovery	Pfizer Inc	UK-351666; UK-356464; UK-356297	Alzheimers disease; Neurodegenerative disease; Parkinsons disease; Peripheral neuropathy	FKBP inhibitors	Antiparkinsonian; Immuno-suppressant
534	**Phase 1 Clinical	Vernalis Group plc	V-2006	Parkinsons disease	Adenosine A2a antagonist	Antiparkinsonian
535	**Discovery	Novavax Inc	vaccine (stroke). Novavax	Cerebrovascular ischemia	Vaccine: CD62E agonist	Neuroprotectant
536	**Research Tool	Royal Gist-Brocades NV	vanoxerine	Schizophrenia: Cocaine addiction	Dopamine uptake inhibitor	Antipsychotic
537	Research Tool	US National Institute on Drug Abuse	Vanoxerine	Schizophrenia	Dopamine uptake inhibitor	Antipsychotic
538	**Discovery	Vasogen Inc	VP-025	Alzheimers disease: Inflammation: Motor neurone disease: Parkinsons disease	Cytokine modulator	Nootropic agent: Anti-inflammatory

	Highest dev. status	Company	Drug	Indication	Mode of action	Drug effect
539	Discovery	Serono: Vertex Pharmaceuticals Inc	VX-799	Neurodegenerative disease: Cardiovascular disease: Cerebral infarction: Cerebrovascular ischemia	Caspase inhibitor	Apoptosis inhibitor: Neuroprotectant: Vasoprotectant: Anti-inflammatory
540	Discovery	Neurocrine Biosciences Inc: Wyeth	WAY-855	Neurodegenerative disease: Psychosis: Schizophrenia: Cerebrovascular ischemia	EAAT modulator: glutamate receptor modulator	Neuroprotectant: Antipsychotic
541	Discovery	Sterling Winthrop Products Inc	WIB-63480-2	Alzheimers disease: Huntingtons chorea: Epilepsy: Cerebrovascular ischemia	NMDA receptor antagonist	Neuroprotectant
542	No Development Reported	Sterling Winthrop Products Inc	WIN-67500	Neurodegenerative disease	Calpain inhibitor	Neuroprotectant
543	No Development Reported	Sterling Winthrop Products Inc	WIN-68100	Neurodegenerative disease	Calpain inhibitor	Neuroprotectant
544	No Development Reported	Sterling Winthrop Products Inc	WIN-69211	Neurodegenerative disease	Calpain inhibitor	Neuroprotectant
545	Phase 3 Clinical	Sanofi-Synthelabo	Xaliprodene	Alzheimers disease	NGF agonist; 5-HT 1a agonist	Neuroprotectant; Nootropic agent
546	**Phase 1 Clinical	Mitsubishi Pharma Corp	Y-931	Schizophrenia	Benzodiazepine agonist	Antipsychotic
547	**Discovery	SK Corp	YKP-1358	Schizophrenia		Antipsychotic
548	Discontinued	Yamanouchi Pharmaceutical Co Ltd	YM-90K	Cerebrovascular ischemia	AMPA receptor antagonist	Neuroprotectant
549	*Pre-registration (Phase 3 Clinical)	Elan Pharmaceuticals Inc	ziconotide	Neurodegenerative disease: Cardiac failure: Cardiovascular disease: Cerebrovascular ischemia: Head injury	Calcium channel blocker, N-type	Neuroprotectant, Analgesic; Vasodilatory agent
550	No Development Reported	Yamanouchi Pharmaceutical Co Ltd	Zonampanel	Cerebrovascular ischemia	AMPA receptor antagonist	Neuroprotectant
551	**Phase 2 Clinical	Shanghai Institute of Materia Medica	ZT-1	Alzheimers disease	Acetylcholinesterase inhibitor	Nootropic agent

Glossary

No Development Reported: No evidence of continuing development has been reported for the past 18 months.

Discontinued: Confirmation from the company source that in-house development has been terminated.

Research Tool: Compounds that are not used as a drug, but needed to investigate the function of a specific compound, which might result in a drug.

Discovery: Late research state, preparation for human testing; adaptation of research chemical synthesis (mg) to larger scale (kg), selection of salt form, selection of galenical form, design of clinical proof of concept studies, definition of endpoints, selection of biomarkers for clinical testing, additional safety testing, IND (investigational new drug) filing, clinical ethical review boards.

Phase 1: Clinical testing; tolerance in humans, repeated dosing, some escalation; proof of therapeutic concept or mechanism using scientific evaluation methods in a limited number of volunteers or patients.

Phase 2: Dose-finding studies, statistics, double blind studies.

Phase 3: Proof of efficacy, comparison to standard therapy, statistics, double blind studies with up to thousands of patients. Final phase of testing before registration and license to market.

Sources

'Investigational Drugs database. Copyright Current Drugs 2004. <http://www.iddb3.com>'

'The Final Neuroprotection Report. Bolt International Healthcare & Pharmaceutical Research. February 2003'

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1: Curr Pharm Des. 2002;8(2):139-45.

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The potential utility of 5-HT1A receptor antagonists in the treatment of cognitive dysfunction associated with Alzheimer s disease.

Schechter LE, Dawson LA, Harder JA.

Wyeth-Ayerst Research, Wyeth Neuroscience, CN 8000, Princeton, NJ 08543-8000, USA.
schechl@war.wyeth.com

The 5-HT1A receptor has been extensively studied over the last two decades. There is a plethora of information describing its anatomical, physiological and biochemical roles in the brain. In addition, the development of selective pharmacological tools coupled with our understanding of psychiatric pathology has lead to multiple hypotheses for the therapeutic utility of 5-HT1A agents and in particular 5-HT1A receptor antagonists. Over the last decade it has been suggested that 5-HT1A receptor antagonists may have therapeutic utility in such diseases as depression, anxiety, drug and nicotine withdrawal as well as schizophrenia. However, a very compelling rationale has been developed for the therapeutic potential of 5-HT1A receptor antagonists in Alzheimer s disease and potentially other diseases with associated cognitive dysfunction. Receptor blockade by a 5-HT1A receptor antagonist appears to enhance activation and signaling through heterosynaptic neuronal circuits known to be involved in cognitive processes and, as such, represents a novel therapeutic approach to the treatment of cognitive deficits associated with Alzheimer s disease and potentially other disorders with underlying cognitive dysfunction.

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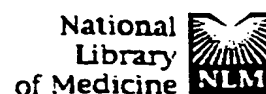
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1: Brain Res Bull. 1992 Dec;29(6):901-4.

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Behavioral profile of the 5HT1A receptor antagonist (S)-UH-301 in rodents and monkeys.

Moreau JL, Griebel G, Jenck F, Martin JR, Widmer U, Haefely WE.

Pharma Division, Preclinical Research, F. Hoffmann-La Roche Ltd, Basel, Switzerland.

The effects of the new 5HT1A receptor antagonist (S)-UH-301 were investigated in several neurological and behavioral tests in rodents and monkeys. By itself, (S)-UH-301 was found to decrease palatable food consumption in rats, to exhibit anticonvulsant activity in mice, and anxiolytic-like properties in two rodent models of anxiety (light-dark test and elevated plus-maze test). (S)-UH-301 antagonized various symptoms and behaviors induced by the selective 5HT1A receptor agonist 8-OH-DPAT, such as lower lip retraction and flat body posture in rats, hyperphagia for palatable food in rats, and displacement activities (considered as indices of anxiety) in squirrel monkeys. These results further characterize (S)-UH-301 as an in vivo active 5HT1A receptor antagonist and suggest that this antagonistic activity might confer the compound with anxiolytic-like properties.

MeSH Terms:

- 8-Hydroxy-2-(di-n-propylamino)tetralin/analogs & derivatives*
- 8-Hydroxy-2-(di-n-propylamino)tetralin/antagonists & inhibitors
- 8-Hydroxy-2-(di-n-propylamino)tetralin/metabolism
- 8-Hydroxy-2-(di-n-propylamino)tetralin/pharmacology*
- Acoustic Stimulation
- Animals
- Brain/metabolism*
- Cerebral Ventricles/drug effects
- Cerebral Ventricles/physiology*
- Conditioning, Operant/drug effects
- Conflict (Psychology)
- Convulsions/physiopathology
- Ergolines/metabolism
- Exploratory Behavior/drug effects*
- Feeding Behavior/drug effects*
- Injections, Intraventricular
- Ketanserin/metabolism
- Learning/drug effects
- Mice

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- Mice, Inbred DBA
- Motor Activity/drug effects*
- N-Methylaspartate/administration & dosage
- N-Methylaspartate/pharmacology*
- Rats
- Receptors, Serotonin/metabolism
- Serotonin/metabolism
- Serotonin Antagonists*

Substances:

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- Receptors, Serotonin
- Serotonin Antagonists
- UH 301
- Serotonin
- N-Methylaspartate
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- Ketanserin
- 8-Hydroxy-2-(di-n-propylamino)tetralin

PMID: 1473022 [PubMed - indexed for MEDLINE]

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Volume 67, Issue 2, 15 August 1999, Pages 213-217

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Articles

Effects of the 5-HT_{1A} Receptor Agonist 8-OH-DPAT on Operant Food Intake in Food-Deprived Pigs

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Received 26 November 1998; accepted 9 March 1999. Available online 10 August 1999.

Abstract

The effects of the 5-HT_{1A} agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) were investigated on operant food intake in food-deprived pigs. In Experiment 1, 8-OH-DPAT (5–20 μ g/kg) administered intravenously (i.v.) 15 min prior to the occurrence of feeding produced a dose-related decrease in operant food intake in pigs that had been fasted overnight. The effects were mainly apparent during the first 30 min after the start of the feeding period. In Experiment 2, 8-OH-DPAT (25 and 50 μ g/kg, i.v.) administered 60 min prior to the occurrence of feeding in pigs that were fasted overnight also produced significant decreases in food intake. The effects were mainly apparent during the first 30–40 min after the start of the feeding period. In Experiment 3, 8-OH-DPAT (20 μ g/kg, i.v.) significantly increased operant feeding in satiated pigs during the first 30 min after administration. These results show that 8-OH-DPAT has complex effects on feeding behaviour in pigs, increasing operant food intake in satiated pigs, while producing a reduction in food intake in food-deprived animals.

Author Keywords: 8-OH-DPAT; Food intake; Satiation; Food deprivation; Pigs

^{EP} To whom requests for reprints should be addressed

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1: Physiol Behav. 2001 May;73(1-2):223-7.

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FULL-TEXT ARTICLE

The differential effects of intravenously administered 8-OH-DPAT on operant food intake in satiated and food-deprived pigs are mediated by central 5-HT(1A) receptors.

Ebenezer IS, Vellucci SV, Parrott RF.

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It has previously been shown that the intravenous administration of the 5-HT (1A) receptor agonist, 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) increases food intake in satiated pigs and decreases food intake in fasted pigs. The present experiments were conducted to investigate the effects of central administration of the 5-HT(1A) receptor antagonist, N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]-N-2-pyridinyl-cyclohexane carbox-amide maleate (WAY 100635), on the stimulant and depressant effects of 8-OH-DPAT on operant food intake in satiated and hungry pigs. In Experiment 1, 8-OH-DPAT (25 microg/kg) produced an increase in operant feeding during the first 30 min following intravenous administration to satiated pigs. The 8-OH-DPAT-induced hyperphagia was completely abolished by pretreatment with WAY 100635 (0.3 mg) administered by intracerebroventricular injection. In Experiment 2, 8-OH-DPAT (25 microg/kg) administered intravenously 15 min prior to the onset of feeding in pigs that had been fasted for 22.5 h produced a decrease in operant food intake, which was most apparent during the first 30 min of the feeding period. The hypophagic effect was completely abolished by pretreatment with WAY 100635 (0.3 mg icv) administered 30 min before the start of the feeding period. In both experiments, WAY 100635 (0.3 mg icv) did not have any significant effects on feeding. The results of the present study extend previous results in the pig and show that both the hyperphagic and the hypophagic effects of 8-OH-DPAT in satiated and fasted pigs, respectively, are mediated by central 5-HT(1A) receptors.

PMID: 11399315 [PubMed - indexed for MEDLINE]

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5-Hydroxytryptamine 1A receptors inhibit cold-induced sympathetically mediated cutaneous vasoconstriction in rabbits

Y. Ootsuka and W. W. Blessing

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5-HT_{1A} receptor agonists lower body temperature. We have investigated whether activation of 5-HT_{1A} receptors inhibits cutaneous sympathetic discharge so that dilatation of the cutaneous vascular bed lowers body temperature by increasing heat transfer to the environment. We measured ear pinna blood flow in conscious rabbits (with chronically implanted Doppler ultrasound flow probes), and postganglionic sympathetic vasomotor nerve activity in anaesthetized rabbits. Recordings from conscious rabbits were made in a cage at 26 °C and the rabbit was then transferred to a cage at 10 °C. The ear pinna Doppler signal fell from $56 \pm 4 \text{ cm s}^{-1}$ in the 26 °C cage to $4 \pm 1 \text{ cm s}^{-1}$ ($P < 0.0001$, $n = 24$) after 30 min in the 10 °C cage, and body temperature increased from 38.8 ± 0.2 to 39.0 ± 0.2 °C ($P < 0.01$, $n = 24$). The 5-HT_{1A} agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT; 0.1 mg kg^{-1} i.v.) reversed the cold-induced fall in ear pinna blood flow (Doppler signal increased from 5 ± 1 to $55 \pm 8 \text{ cm s}^{-1}$, $P < 0.001$, $n = 7$) within 5 min when administered 30 min after transfer to the 10 °C cage, and prevented the fall in ear pinna blood flow when administered before the rabbit was transferred to the 10 °C cage. Body temperature decreased after administration of 8-OH-DPAT. These changes were abolished by the specific 5-HT_{1A} antagonist WAY-100635 (0.1 mg kg^{-1} i.v.). In anaesthetized rabbits, 8-OH-DPAT (0.1 mg kg^{-1} i.v.) reduced resting postganglionic cutaneous sympathetic vasomotor discharge, and prevented the increase normally elicited by cooling the trunk. Our experiments constitute the first demonstration that activation of 5-HT_{1A} receptors powerfully inhibits cold-induced increases in cutaneous sympathetic vasomotor discharge, thereby dilating the cutaneous vascular bed and increasing transfer of heat to the environment.

(Received 27 May 2003; accepted after revision 3 August 2003; first published online 8 August 2003)

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Identification of the different 5-hydroxytryptamine (5-HT) receptor subtypes has facilitated our understanding of the contribution of 5-HT to the regulation of body temperature. Activation of 5-HT_{1A} receptors decreases body temperature (Hjorth, 1985; Gudelsky *et al.* 1986; Cryan *et al.* 1999). Activation of 5-HT_{2A} receptors increases body temperature (Gudelsky *et al.* 1986; Löscher *et al.* 1990; Mazzola-Pomietto *et al.* 1995). However, the relevant neuro-anatomical pathways and underlying neurotransmitter mechanisms mediating these effects remain to be elucidated. The task is especially complicated because 5-HT alters so many psychological, behavioural and physiological variables (Barnes & Sharp, 1999). Pharmacological and physiological studies of the mechanisms underlying the temperature effects of agents acting at 5-HT_{1A} receptors often focus on body temperature *per se*, without determining the relative contributions of heat production and/or heat loss to the temperature equation.

Similar considerations apply to neuroanatomical studies. Interest in the role of 5-HT in temperature control has

focused on upper brainstem and forebrain 5-HT-innervated regions. Much less attention has been paid to possible contributions of the thermoregulatory role of 5-HT via regulation of heat exchange with the environment through the cutaneous circulation, i.e. on heat dissipation rather than heat production. Even when temperature studies have focused on 5-HT neurons in the medullary raphe region, interpretation of the results has emphasized possible ascending projections of the cells (Dickenson, 1977; Berner *et al.* 1999), rather than descending projections to cutaneous sympathetic preganglionic neurons in the spinal cord. Central neuroanatomical organization of the descending central control of the cutaneous circulation includes a brainstem relay in raphe magnus/pallidus and the parapyramidal region of the medulla oblongata (Blessing & Nalivaiko, 2000; Nalivaiko & Blessing, 2001; Tanaka *et al.* 2002). Neurons in this medullary region include the B1–B3 bulbospinal cells that synthesize 5-HT (Loewy, 1981; Steinbusch, 1981; Skagerberg & Bjorklund, 1985; Nicholas *et al.* 1992). Transneuronal intra-axonal tracing experiments in rats show that 5-HT neurons are amongst

the early wave of virus-containing cells after injection of virus into the tail (Smith *et al.* 1998), which is the principal heat-exchanging cutaneous vascular bed in this species. 5-HT_{1A} receptors have been demonstrated on raphe/parapyramidal spinally projecting neurons present in the medulla oblongata (Helke *et al.* 1997). Thus 5-HT_{1A} agonists could lower body temperature by inhibiting the action of cutaneous premotor sympathetic neurons, including 5-HT neurons located in this region.

We have now determined whether activation of 5-HT_{1A} receptors by the specific agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) (Arvidsson *et al.* 1987) can reduce body temperature by increasing cutaneous blood flow, thereby facilitating transfer of heat from the body. In conscious rabbits we first induced vasoconstriction of the ear pinna vascular bed by exposing the animals to a cold environment. We then determined whether 5-HT_{1A} receptor activation reverses this physiologically induced, sympathetically mediated cutaneous vasoconstriction. In anaesthetized rabbits we then directly measured postganglionic cutaneous sympathetic nerve activity, determining whether stimulation of 5-HT_{1A} receptors inhibits ongoing cutaneous sympathetic discharge activity and reduces cold-induced cutaneous sympathetic discharge. We determined whether WAY-100635, a specific 5-HT_{1A} antagonist (Forster *et al.* 1995), reverses and/or prevents the changes induced by 8-OH-DPAT.

METHODS

Ear pinna blood flow in conscious unrestrained rabbits

Experiments were performed on 31 conscious unrestrained New Zealand White rabbits (2.5–4.5 kg) purchased from Nanowie Rabbit Farm, Torquet, Australia. Rabbits were frequently handled and transferred between cages in the animal house. Each rabbit was used in up to five of the experimental conditions, with at least 3 days elapsing between each experiment. Experimental procedures were approved by the Flinders University Animal Welfare Committee. For implantation of probes, rabbits were anaesthetized with midazolam and hypnorm (0.4 mg kg⁻¹ and 0.3 mg kg⁻¹ i.m. respectively), a chronically implanted Doppler ultrasonic flow probe (Iowa Doppler Products, IA, USA) was positioned around the central ear pinna artery, and a telemetric temperature probe (Data Sciences International, St Paul, MN, USA) was implanted intraperitoneally (Pedersen & Blessing, 2001). At the conclusion of the surgical procedures each rabbit was given carprofen (4 mg kg⁻¹ s.c.; Pfizer Pty Ltd, West Ryde, NSW, Australia) as an analgesic agent. Rabbits were given supplemental vegetables in the diet for 1 week after surgery. All animals ate, drank and moved freely on the first post-operative day.

Animals were studied in temperature-controlled cages equipped with a swivel device and flexible cable that attached to a socket fixed to the animal's skull, so that blood flow recordings could be made while the conscious animal moved freely within the cage. Food and water were continuously available. At the end of the experiments rabbits were killed by intravenous injection of 2 ml of pentobarbitone sodium (325 mg ml⁻¹).

In initial experiments, the set-point of the temperature-controlled cage was reduced from 26 to 15°C after a 30 min control recording period. Because it took 20–30 min to reduce the cage temperature from 26 to 15°C, subsequent experiments were carried out by transferring the animal from the 26°C cage to a second cage already maintained at 10°C, with the lower temperature chosen so that cold-induced cutaneous vasoconstriction was more marked. Ear pinna blood flow and body temperature were assessed throughout the experiment, except for a brief period during transfer from the 26°C cage to the 10°C cage. Temperature and Doppler signals were processed (Triton Technology, San Diego, CA, USA) and digitized (40 and 2 Hz for flow and temperature signals, respectively) using PowerLab and Chart software (ADInstruments, Sydney, Australia) and a Macintosh computer.

Postganglionic cutaneous vasculature sympathetic discharge in anaesthetized rabbits

Experiments were performed on six male New Zealand White rabbits (2.5–3.5 kg). Animals were given a single dose of methylscopolamine bromide (50 µg i.v.) to reduce airway secretions, and then anaesthetized with urethane (Sigma Chemical Co., Castle Hill, Australia; 1.5 g kg⁻¹ i.v., infused via the right ear marginal vein over 20 min). Fur was shaved from the trunk and neck. An endotracheal tube was inserted via a tracheostomy. The left femoral artery and vein were cannulated for measurement of systemic arterial pressure and for intravenous drug infusion, respectively.

The animal was mounted prone in a Kopf stereotaxic frame, with a water jacket positioned around the trunk. Warm water (36–48°C) was circulated (1–2 l min⁻¹) through the water jacket to maintain body temperature between 38 and 39°C. A thermocouple was attached to the abdominal skin under the water jacket to monitor skin temperature. Another thermocouple was inserted 6 cm into the rectum to measure core body temperature. Circulating cold water (10–20°C) through the jacket for 5–12 min lowered skin temperature and this was followed by a delayed fall in body (rectal) temperature. Recirculation of warm water reversed these changes.

The left cervical sympathetic trunk was exposed from the dorsolateral aspect and the intact nerve was placed across a pair of silver-wire electrodes. A small (approximately 0.1 mm diameter) nerve fascicle was dissected from the central ear branch of the posterior auricular artery approximately 3 cm from the base of the ear. The distal end of the nerve was cut and the nerve was placed over bipolar silver–silver chloride wire electrodes. The nerves were covered with a mixture of paraffin oil and Vaseline to prevent drying. Multiunit nerve action potential recordings were made using a Neurolog NL100 preamplifier and Neurolog NL104 amplifier (NL125 filters 100–1000 Hz) (Digitimer Ltd, Hertfordshire, UK). The noise level was determined from inspection of the signal between bursts of discharge and confirmed at the end of the experiment by abolishing all postganglionic sympathetic discharge with hexamethonium (see below). All recorded signals, including the raw nerve signal, were recorded on videotape for offline analysis. A Grass 7P10B signal conditioning unit (Grass Telefactor, West Warwick, RI, USA), was used to full wave rectify the raw nerve signal bursts that exceeded the noise level, and the supra-threshold signal was integrated with a Neurolog NL705 (root mean square, time constant 500 ms).

On completion of the surgery animals were neuromuscularly blocked with vecuronium bromide ($1\text{--}1.5\text{ mg kg}^{-1}$ i.v.) and mechanically ventilated with 100% oxygen. End tidal CO₂ (Normcap CO₂ monitor, Datex, Helsinki, Finland) was kept at 30–40 mmHg. After neuromuscular block, adequate anaesthesia was determined by the absence of any increase in arterial pressure in response to possibly painful procedures and by ensuring the absence of a withdrawal reflex to paw squeeze during periods when the return of active respiratory effort indicated that neuromuscular block was no longer present. If anaesthesia was inadequate, supplemental urethane (150 mg kg^{-1} i.v.) was administered over 5 min. When anaesthesia was adequate, supplemental vecuronium bromide (0.5 mg kg^{-1} i.v.) was administered to maintain neuromuscular block.

The cervical sympathetic trunk was electrically stimulated with a single rectangular pulse of 0.5 ms with current strength ($50\text{--}500\text{ }\mu\text{A}$) at twice the threshold level required to produce an evoked potential in the ear pinna cutaneous sympathetic nerve. A peristimulus time histogram (16 sweeps) was constructed to confirm the sympathetic nature of the ear pinna nerve from which recordings were being made, and to confirm that the nerve was in place on the electrodes during periods of low or absent spontaneous activity. We then measured the increase in nerve discharge elicited by perfusing cold water through the jacket. After recovery following reperfusion of warm water, when nerve discharge was stable, we administered 8-OH-DPAT (0.1 mg kg^{-1} i.v.). The effect on resting nerve discharge was assessed 5 min after the injection. Responses to electrical stimulation of the cervical sympathetic trunk and to trunk cooling were again assessed. In three of six animals we then administered WAY-100635 (0.1 mg kg^{-1} i.v.) and determined the effect on ear pinna sympathetic discharge. In all animals, at the end of the experiments, the ear pinna sympathetic nerve response to stimulation of the left cervical sympathetic trunk was confirmed after injection of the ganglionic blocking agent hexamethonium bromide (50 mg kg^{-1} i.v.). At the end of the experiments rabbits were killed by intravenous injection of 2 ml of pentobarbitone sodium (325 mg ml^{-1}).

Pharmacological agents

All drugs were administered intravenously; into the marginal ear vein contralateral to the implanted ear pinna Doppler probe in conscious rabbits and into the femoral vein in anaesthetized rabbits. WAY-100635, 8-OH-DPAT and hexamethonium bromide were purchased from Sigma Chemical Company (Castle Hill, Australia) and dissolved in Ringer solution.

Statistical analysis

Data were analysed with Chart (ADInstruments, Sydney, Australia), IgorPro (WaveMetrics, Lake Oswego, OR, USA) and Statview (SAS Institute, Cary, NC, USA) software. Conscious unrestrained rabbits have variable 'baseline' pulsatile ear pinna blood flow signals, with episodic sudden falls from high levels to near-zero levels, and gradual return to the previous high level within approximately 1 min (Yu & Blessing, 1997). For each animal in a particular condition, we measured mean ear pinna blood flow and body temperature averaged over a 2 min period when the baseline flow was not affected by these alerting responses. Examples of the time period selected for measurement during the control period are indicated as a bar in the graph of ear pinna blood flow for each of the four flow traces shown in Figs 1 and 2. Details of other measurement times are given in the

appropriate Results section. For analysis of data from anaesthetized rabbits, integrated nerve activity signal, and arterial pressure, core body temperature, skin temperature and end-tidal CO₂ were digitized with PowerLab (100 Hz) and displayed on a Macintosh computer.

Group data were analysed by repeated measures analysis of variance, with comparison of particular post-injection values with each other and with the corresponding control values. Factorial analysis of variance was used to compare values from corresponding time points in vehicle and drug-treated animals. Fisher's protected *t* test was used to determine significant differences, with the significance threshold set at the 0.05 level.

RESULTS

Ear pinna blood flow and body temperature in conscious rabbits

In control experiments to determine whether the process of transfer from one cage to another causes stress-related changes in ear pinna blood flow, rabbits were transferred from the 26°C cage to a second similar cage, also maintained at 26°C. The mean Doppler ear pinna blood flow signal was $65 \pm 9\text{ cm s}^{-1}$ before transfer and $65 \pm 10\text{ cm s}^{-1}$ 30 min after transfer ($P > 0.05$, $n = 5$). Corresponding body temperature values were 37.8 ± 0.5 and $38.1 \pm 0.5^\circ\text{C}$ ($P > 0.05$, $n = 5$). Thus the process of cage transfer did not, of itself, cause any significant change in ear pinna blood flow or body temperature.

In all rabbits, after transfer from the 26°C cage to the second cage maintained at 10°C, mean ear pinna blood flow fell and stabilized at a very low level within 15 min (Figs 1A and 2A). Effects on ear pinna blood flow and body temperature of a 30 min exposure to 10°C after abrupt transfer from the 26°C cage were statistically assessed by combining the data from the 24 rabbits in the different conditions (Table 1) that received no treatment before transfer to the 10°C cage. Ear pinna blood flow fell from $56 \pm 4\text{ cm s}^{-1}$ in the 26°C cage to $4 \pm 1\text{ cm s}^{-1}$ ($P < 0.0001$, $n = 24$) after 30 min in the 10°C cage. Body temperature slightly increased (Fig. 1B), from 38.77 ± 0.16 to $39.04 \pm 0.18^\circ\text{C}$, during the first 30 min after transfer from the 26°C cage to the 10°C cage ($+0.27 \pm 0.08^\circ\text{C}$, $n = 24$, $P < 0.01$).

Effect of drug treatment on ear pinna blood flow and body temperature in rabbits exposed to a cold environment

Treatment with 8-OH-DPAT after gradual reduction in cage-temperature from 26 to 15°C. Administration of 0.01 mg kg^{-1} 8-OH-DPAT, 20 min after cage temperature was reduced to 15°C and ear pinna blood flow had fallen to a very low level, did not significantly change ear pinna blood flow (Table 1A). Subsequent administration of 0.1 mg kg^{-1} 8-OH-DPAT increased ear pinna blood flow within a few minutes of administration, restoring flow to the levels initially observed in the warm environment (Table 1A).

Treatment with 8-OH-DPAT or vehicle after transfer from the 26°C cage to the 10°C cage. Within 3 min of injection of 8-OH-DPAT (0.1 mg kg^{-1}), administered 30 min after transfer from the 26°C cage to the 10°C cage, ear pinna blood flow rapidly and substantially increased from the very low cold-induced level to a level similar to that observed when the animal was in the 26°C chamber (Fig. 1A and Table 1B). The 8-OH-DPAT-induced increase in flow lasted approximately 20 min after which time flow once again decreased to low levels (Fig. 1A and Table 1B). When a higher dose of 8-OH-DPAT (0.5 mg kg^{-1}) was administered 30 min after the previous 0.1 mg kg^{-1} dose, ear pinna blood flow increased again and remained at a high level for the duration of an additional 30 min

observation period, so that at the end of this time ear pinna flow was $53 \pm 5 \text{ cm s}^{-1}$, significantly greater than the flow value after 30 min cold exposure ($P < 0.01$) and not significantly different from the flow value recorded at 26°C before transfer to the cold ($P > 0.05$, $n = 6$).

There was a small rise in body temperature during the first 30 min after transfer from the 26°C cage to the 10°C cage (Fig. 1A and Table 1B). In the 30 min period after administration of 8-OH-DPAT (0.1 mg kg^{-1}), body temperature decreased by approximately 0.5°C (Fig. 1A and Table 1B).

In a separate group of rabbits, Ringer vehicle (2 ml) administered 30 min after transfer from the 26°C cage to

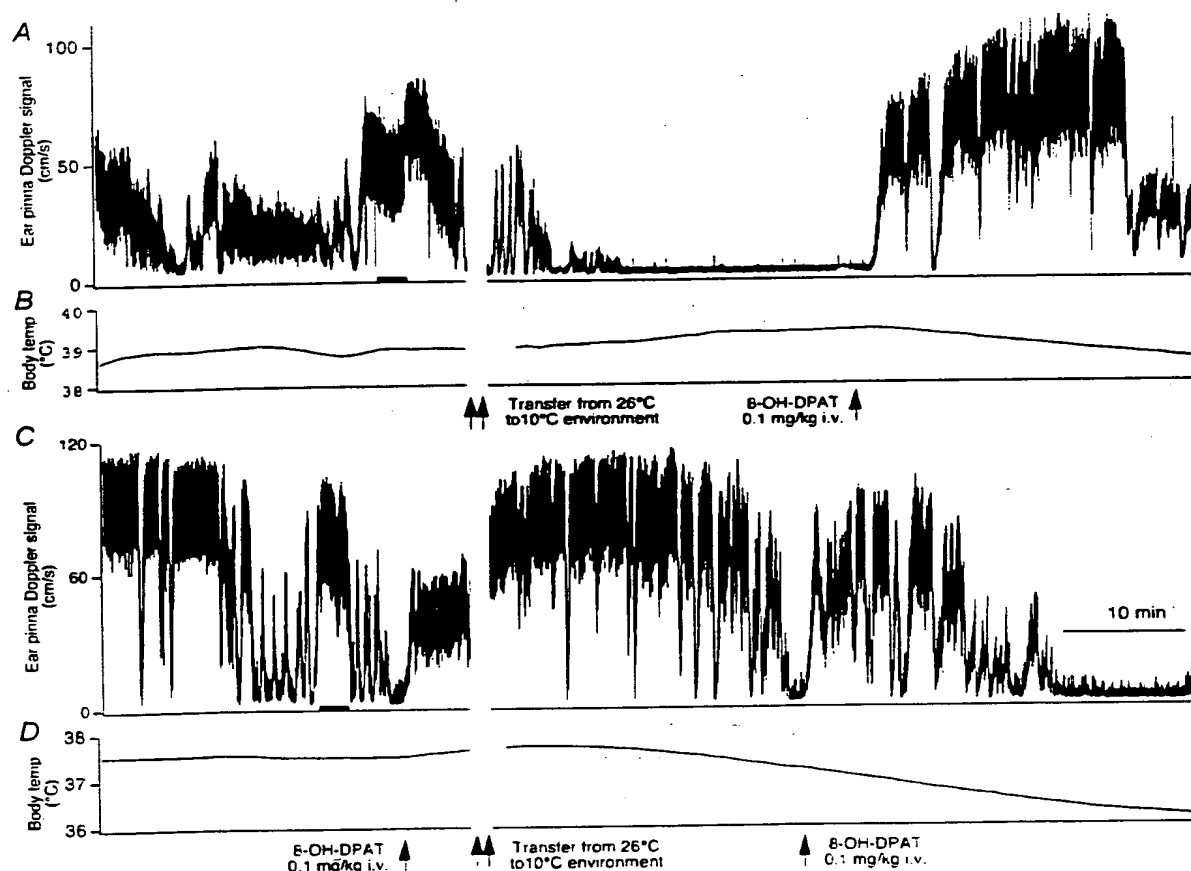


Figure 1. 8-Hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) reverses and prevents cold-induced ear pinna vasoconstriction

Records of ultrasonic Doppler signal measuring phasic ear pinna blood flow (A and C) and body temperature (B and D) in conscious freely moving rabbits. The initial 30 min recording was obtained with the rabbit in a 26°C cage. At the time point indicated by the double vertical arrows the animal was transferred to a 10°C cage. 8-OH-DPAT (0.1 mg kg^{-1} i.v.) was administered at the time indicated by the single vertical arrows. A and B, 8-OH-DPAT was administered 30 min after transfer to the 10°C cage. C and D, 8-OH-DPAT was administered before transfer to the 10°C cage, and then again 30 min after transfer. Records in A and C, both before and after 8-OH-DPAT, exhibit sudden alerting-related falls in ear pinna blood flow, with return to the pre-fall level in approximately 1 min. The 10 min time bar in C applies to all panels. The 2 min bar in the control periods of A and C indicates the when the mean flow was measured in these records.

Table 1. Modification of cold-induced changes in cutaneous blood flow and body temperature by 5-HT_{1A} receptors

A. Cage temperature reduced gradually from 26 to 15°C, then 8-OH-DPAT						
	Cage temperature 26°C	After 20 min at cage temperature 15°C	5 min after 8-OH-DPAT (0.01 mg kg ⁻¹)	5 min after 8-OH-DPAT (0.1 mg kg ⁻¹)		
Ear pinna flow signal (cm s ⁻¹)	44 ± 6 (7)	6 ± 2 (7)*	10 ± 4 (6)**	55 ± 8 (7)‡§		
B. Rabbit transferred from 26°C cage to 10°C cage, then 8-OH-DPAT or vehicle						
	26°C cage	30 min after transfer to 10°C cage	5 min after 8-OH-DPAT (0.1 mg kg ⁻¹) or vehicle	30 min after 8-OH-DPAT (0.1 mg kg ⁻¹) or vehicle		
8-OH-DPAT						
Ear pinna blood flow (cm s ⁻¹)	56 ± 7 (7)	5 ± 1 (7)*	55 ± 8 (7)‡‡	5 ± 1 (6)*		
Body temperature (°C)	38.8 ± 0.3 (7)	9.2 ± 0.4 (7)*	39.2 ± 0.4 (7)	38.7 ± 0.4 (7)‡‡		
Vehicle						
Ear pinna blood flow (cm s ⁻¹)	47 ± 10 (5)	5 ± 2 (5)*	3 ± 1 (5)*§	2 ± 1 (5)*		
Body temperature (°C)	39.1 ± 0.2 (6)	39.4 ± 0.2 (6)‡	39.2 ± 0.4 (6)‡	39.2 ± 0.1 (6)‡		
C. 8-OH-DPAT in 26°C cage, transfer to 10°C cage, second 8-OH-DPAT injection after 30 min						
	26°C cage, before 8-OH-DPAT	26°C cage 5 min after 8-OH-DPAT (0.1 mg kg ⁻¹)	5–30 min after transfer to 10°C cage	60 min after transfer to 10°C cage		
Ear pinna flow signal (cm s ⁻¹)	78 ± 7 (7)	52.0 ± 5 (7)*	35 ± 7 (7)‡	2 ± 1 (7)†		
Body temperature (°C)	37.9 ± 0.4 (7)	38.0 ± 0.4 (7)	37.6 ± 0.3 (7)‡	37.0 ± 0.3 (7)‡		
D. Transfer from 26°C cage to 10°C cage, then 8-OH-DPAT, then WAY-100635						
	26°C cage	30 min after transfer to 10°C cage	5 min after 8-OH-DPAT (0.1 mg kg ⁻¹)	5 min after WAY-100635 (0.1 mg kg ⁻¹)	30 min after WAY-100635	15 min after transfer back to 26°C cage
Ear pinna flow signal (cm s ⁻¹)	51 ± 8 (6)	3 ± 1 (6)*	51 ± 10 (6)†‡	4 ± 1 (6)*	4 ± 1 (6)*§	41 ± 8 (6)‡
Body temperature (°C)	38.4 ± 0.4 (5)	38.4 ± 0.4 (5)‡	38.3 ± 0.4 (5)‡	38.2 ± 0.4 (5)‡	38.7 ± 0.5 (5)‡	39.5 ± 0.6 (5)*
E. Transfer from the 26°C cage to the 10°C cage, then WAY-100635 and then 8-OH-DPAT						
	26°C cage	30 min after transfer to 10°C cage	5 min after WAY-100635 (0.1 mg kg ⁻¹)	5 min after 8-OH-DPAT (0.1 mg kg ⁻¹)	30 min after 8-OH-DPAT (0.1 mg kg ⁻¹)	26°C cage
Ear pinna flow signal (cm s ⁻¹)	69 ± 8 (6)	5 ± 1 (6)*	5 ± 1 (6)*†	4 ± 1 (6)*†	5 ± 1 (6)*†	44 ± 11 (6)§
Body temperature (°C)	38.7 ± 0.4 (6)	39.1 ± 0.4 (6)‡	39.3 ± 0.4 (6)‡	39.3 ± 0.4 (6)‡	39.5 ± 0.4 (6)‡	39.5 ± 0.6 (6)‡
F. WAY-100635 given in 26°C cage, then rabbit transferred to 10°C cage, then 8-OH-DPAT						
	26°C cage before WAY-100635	26°C cage 5 min after WAY-100635 (0.1 mg kg ⁻¹)	30 min after transfer to 10°C cage	5 min after 8-OH-DPAT (0.1 mg kg ⁻¹)	30 min after 8-OH-DPAT (0.1 mg kg ⁻¹)	26°C cage
Ear pinna flow signal (cm s ⁻¹)	51 ± 5 (5)	45 ± 5 (5)§	6 ± 1 (5)*	7 ± 1 (5)*‡	6 ± 1 (5)*‡†	25 ± 5 (5)*†
Body temperature (°C)	39.1 ± 0.6 (5)	39.2 ± 0.5 (5)§	39.3 ± 0.5 (5)§	39.3 ± 0.5 (5)§	39.4 ± 0.4 (5)§	39.5 ± 0.6 (5)§

Effect on ear pinna blood flow and body temperature (mean ± S.E.M.) of intravenous administration of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) or WAY-100635, either in a 26°C cage with gradual reduction of cage temperature to 15°C (A) or with transfer of the rabbit from the 26°C cage to a second cage maintained at 10°C (B–F). The heading of each subsection describes the experimental condition for that subsection. Explanation of symbols: A, * significantly different from 26°C control value, $P < 0.01$; † not significantly different from 20 min post transfer value, $P > 0.05$; ‡ significantly different from 20 min post transfer value, $P < 0.01$; and § not significantly different from 26°C control value, $P > 0.05$. B, * significantly different from 26°C control value, $P < 0.01$; † significantly different from 30 min post transfer value, $P < 0.01$; ‡ not significantly different from 26°C control value, $P > 0.05$; and § not significantly different from 30 min post transfer value, $P > 0.05$. C, * significantly different from 26°C control value before 8-OH-DPAT, $P < 0.05$; † significantly different from 26°C control value after 8-OH-DPAT, $P < 0.01$; and ‡ not significantly different from 26°C control value after 8-OH-DPAT, $P > 0.05$. D, * significantly different from 26°C control value, $P < 0.01$; † significantly different from 30 min post transfer value, $P < 0.01$; ‡ not significantly different from 26°C control value, $P > 0.05$; and § not significantly different from value 5 min after WAY-100635, $P > 0.05$. E, * significantly different from 26°C control value, $P < 0.01$; † not significantly different from 30 min post transfer value, $P > 0.05$; and ‡ not significantly different from 26°C control value, $P > 0.05$. F, * significantly different from 26°C control value after WAY-100635, $P < 0.01$; † significantly different from 30 min post transfer value, $P > 0.01$; ‡ not significantly different from 30 min post transfer value, $P > 0.05$; and § not significantly different from 26°C control value after WAY-100635, $P > 0.05$.

the 10°C cage did not change ear pinna blood flow (Table 1B). In these animals there was no significant change in body temperature during the first 30 min after transfer to the 10°C cage (Table 1B).

Treatment with 8-OH-DPAT before transfer from the 26°C cage to the 10°C cage. Administration of 8-OH-DPAT (0.1 mg kg^{-1}) at 26°C caused a small fall in ear pinna blood flow which lasted for the duration of the 5 min period before the rabbit was transferred to the 10°C cage. (Fig. 1C and Table 1C). In these rabbits the mean ear pinna blood flow for the period 5–30 min after transfer to the 10°C cage was $35 \pm 7 \text{ cm s}^{-1}$ ($n = 7$), significantly greater ($P < 0.01$) than $7 \pm 2 \text{ cm s}^{-1}$ ($n = 12$), the corresponding value in rabbits receiving 8-OH-DPAT or vehicle 30 min after transfer to the 10°C cage, but with no treatment before transfer to the cold. In rabbits treated in the 26°C cage with 8-OH-DPAT, body temperature decreased during the first 30 min after transfer to the 10°C cage ($-0.42 \pm 0.15^\circ\text{C}$, $P < 0.01$, $n = 7$). In contrast, in rabbits

receiving no treatment before transfer to the cold (combined groups), body temperature slightly increased after transfer ($+0.27 \pm 0.08^\circ\text{C}$, $n = 24$, $P < 0.01$). Therefore treatment with 8-OH-DPAT before transfer to the cold substantially prevented cold-induced ear pinna vasoconstriction, and increased the amount of heat transferred from the body to the cold environment.

Treatment with 8-OH-DPAT after transfer from the 26°C cage to the 10°C cage, and then treatment with WAY-100635. In rabbits transferred from the 26°C cage to the 10°C cage, administration of 8-OH-DPAT (0.1 mg kg^{-1}) 30 min after transfer reversed cold-induced ear pinna vasoconstriction (Fig. 2A and Table 1D) in a manner very similar to that observed in a previous experiment (Fig. 1A and Table 1B). When WAY-100635 (0.1 mg kg^{-1}) was administered 10 min after 8-OH-DPAT, ear pinna blood flow fell promptly to a very low level and remained at a very low level for the 30 min period during which the rabbit was kept in the 10°C cage. The initial rapid fall in ear pinna

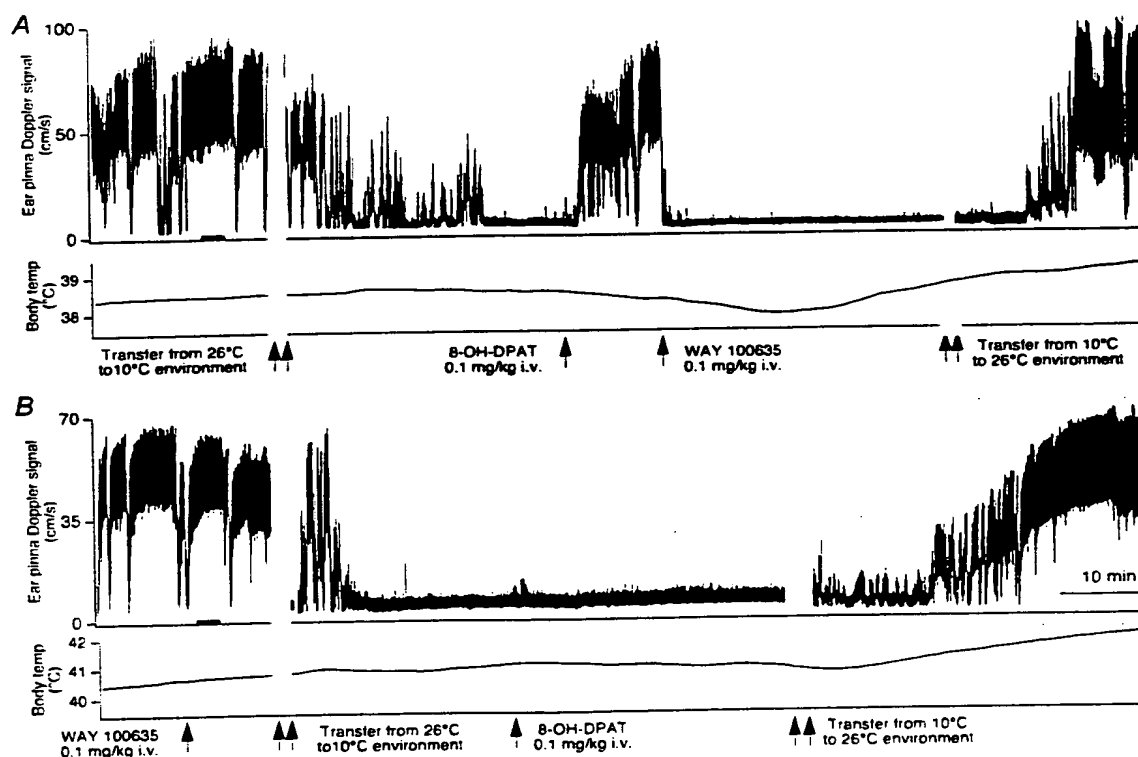


Figure 2. WAY-100635 prevents and reverses the vasodilating action of 8-OH-DPAT

Records of ultrasonic Doppler signal measuring phasic ear pinna blood flow (A and C) and body temperature (B and D) in conscious freely moving rabbits. The initial 20 min recording was obtained with the rabbit in a 26°C cage. At the time point indicated by the first pair of double vertical arrows the animal was transferred to a 10°C cage. At the time point indicated by the second pair of double vertical arrows the animal was transferred back to 26°C cage. 8-OH-DPAT (0.1 mg kg^{-1}) or WAY-100635 (0.1 mg kg^{-1} i.v.) was administered at the times indicated by the single vertical arrow. Alerting-related falls also occurred during the brief handling period required for intravenous injection. This explains why the vasoconstricting effect of WAY-100635 seems so abrupt in A. The 10 min time bar applies to all panels. The 2 min bar in the control periods of A and C indicates the when the mean flow was measured in these records.

blood flow after WAY-100635 (Fig. 2A) reflects the alerting-related effect associated with the injection procedure. After the rabbit was transferred back to the 26°C cage, within 15 min ear pinna blood flow returned to the levels originally observed in this cage (Fig. 2A and B, and Table 1D). In this subgroup of rabbits, there was no significant change in body temperature during the 30 min in the 10°C cage, nor did temperature change after administration of 8-OH-DPAT (Table 1D).

Treatment with WAY-100635 after transfer from the 26°C cage to the 10°C cage, and then treatment with 8-OH-DPAT. In rabbits transferred from the 26°C cage to the 10°C cage, ear pinna blood flow fell to very low levels in the usual manner. Administration of WAY-100635 (0.1 mg kg⁻¹) 30 min after transfer did not alter ear pinna

blood flow (Table 1E), nor did subsequent administration of 8-OH-DPAT (0.1 mg kg⁻¹). When rabbits were returned to the 26°C cage, ear pinna blood flow increased to a level not significantly different from the level previously observed in this cage (Table 1E). In this subgroup of rabbits body temperature did not significantly change during the 30 min exposure to cold, nor did it change significantly during the 30 min period after administration of WAY-100635 and then 8-OH-DPAT (Table 1E).

Treatment with WAY-100635 before transfer from the 26°C cage to the 10°C cage, and then treatment with 8-OH-DPAT. Ear pinna blood flow did not change when WAY-100635 (0.1 mg kg⁻¹) was administered 5 min before the end of the 30 min control period in the 26°C cage. After transfer to the 10°C cage, ear pinna blood flow

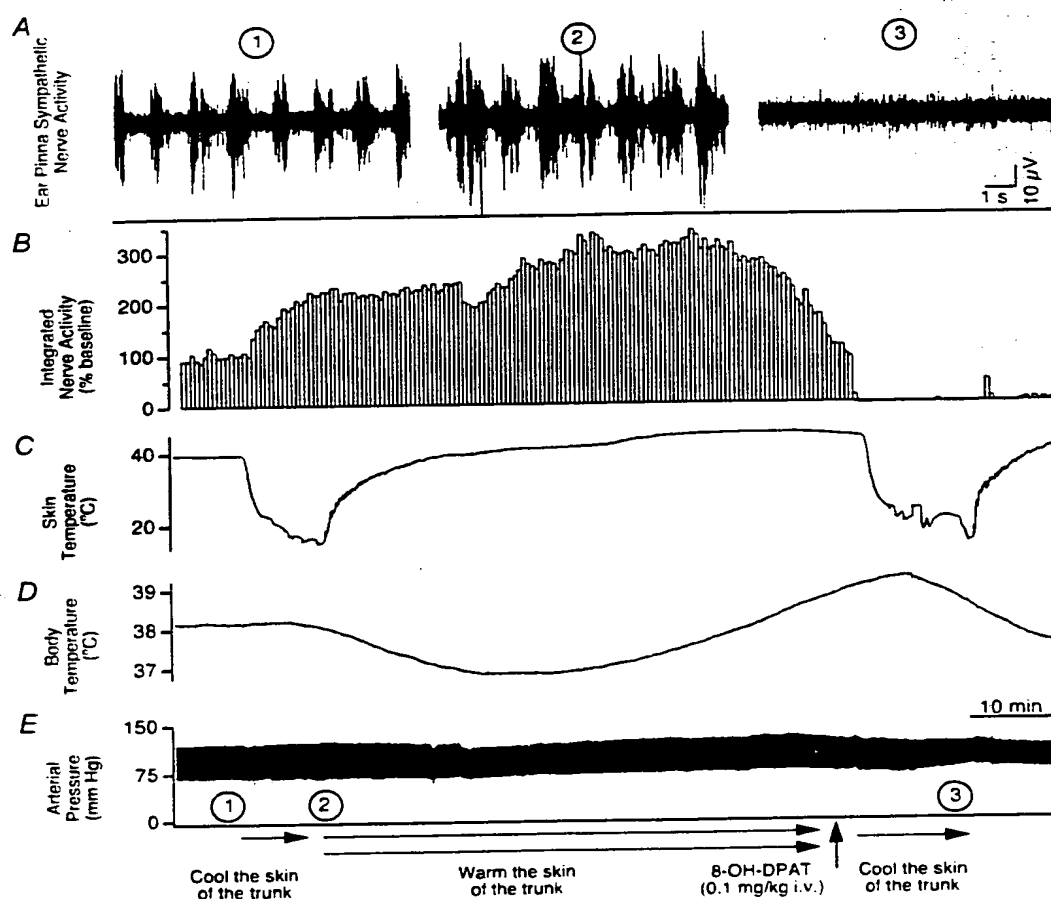


Figure 3. 8-OH-DPAT inhibits cutaneous sympathetic nerve discharge

Recording of ear pinna sympathetic nerve discharge (A), 30 s bins (B), skin temperature (C), body temperature (D) and arterial pressure (E) from an anaesthetized rabbit. The circled numbers (1–3) in A correspond to the circled numbers on the X axis in E, indicating the time period during which the nerve recording shown in A was made. The trunk skin was cooled during the time indicated by the single horizontal arrows and warmed during the period indicated by the double horizontal arrow. 8-OH-DPAT (0.1 mg kg⁻¹ i.v.) was administered at the time shown by the vertical arrow. The 10 min time base bar in E also applies to B, C and D.

fell to very low levels in the usual manner (Fig. 2B and Table 1F). Subsequent administration of 8-OH-DPAT did not alter ear pinna blood flow at either 5 or 30 min after injection (Fig. 2B and Table 1F). When the rabbit was returned to the warm 26°C cage, ear pinna blood flow increased, although the level reached in the group data was not as high as observed during the initial control period (Table 1F). Body temperature did not change significantly from the control value recorded in the 26°C cage at any stage (Table 1F).

Cutaneous sympathetic nerve activity in anaesthetized rabbits

When stable nerve recordings were obtained, rabbits were maintained with warm water circulating through the water jacket so that skin temperature was $39.4 \pm 0.4^\circ\text{C}$ and body (rectal) temperature was $38.6 \pm 0.2^\circ\text{C}$. The identity of the nerve fibres as sympathetic was verified by testing the response to electrical stimulation of the intact cervical sympathetic trunk. Single pulse stimulation (50–500 μA , 0.5 ms) of the cervical sympathetic trunk in six rabbits increased the discharge of the ear pinna sympathetic nerve with a response latency of 95 ± 5 ms and response duration of 72 ± 10 ms. The conduction velocity from stimulation

site to recording site was 1.1 ± 0.1 ms. The maximum amplitude of the response was $25 \pm 5 \mu\text{V}$.

The trunk skin of the rabbit was then cooled by circulating cold water (10°C) through the water jacket. This procedure rapidly lowered skin temperature to $23.5 \pm 2.3^\circ\text{C}$ and caused a delayed fall in core temperature to $37.9 \pm 0.3^\circ\text{C}$. The cooling procedure increased ear sympathetic nerve discharge to $172 \pm 19\%$ of pre-cooling level ($P < 0.01$, $n = 5$). Records from one rabbit are shown in Fig. 3. When the animal was rewarmed by re-introducing the warm water into the jacket, nerve activity gradually declined towards the pre-cooling baseline level. When nerve discharge was again reasonably stable, we injected 8-OH-DPAT (0.1 mg kg^{-1} i.v.). Arterial pressure was unchanged by this procedure (95 ± 6 mmHg before and 93 ± 5 mmHg 5 min after 8-OH-DPAT, $P > 0.05$, $n = 6$). Administration of 8-OH-DPAT caused nerve activity to fall, within a minute or so of the injection (Fig. 3) so that 5 min after the injection nerve activity was $5 \pm 2\%$ ($n = 6$, $P < 0.01$) of pre-injection discharge level. When the rabbit was cooled 5–10 min after administration of 8-OH-DPAT, the increase in sympathetic nerve discharge elicited by the cooling procedure was reduced to $14 \pm 8\%$ ($n = 6$, $P < 0.01$) of the

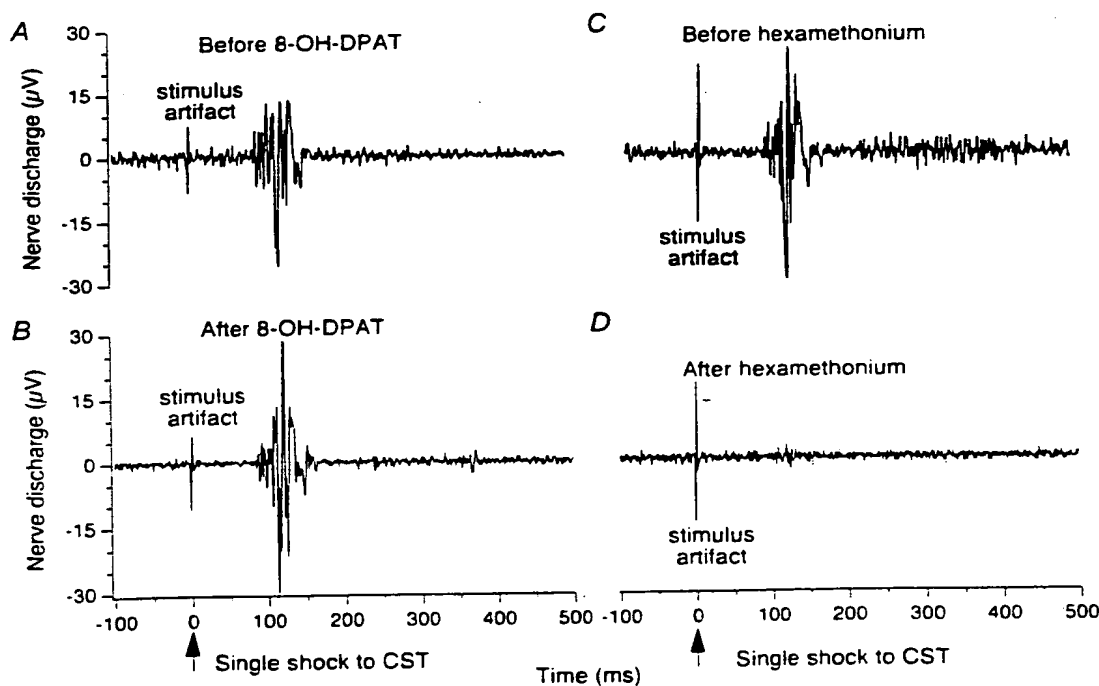


Figure 4. Ear pinna sympathetic nerve discharge evoked by stimulation of cervical sympathetic trunk

Peristimulus histograms (average of 16 sweeps) of ear pinna sympathetic nerve discharge evoked by single shock electrical stimulation of the ipsilateral cervical sympathetic trunk (CST), administered at time zero. A and B demonstrate that the evoked response is unaffected 5 min after 8-OH-DPAT (0.1 mg kg^{-1} i.v.). C and D demonstrate that the evoked response is abolished 5 min after hexamethonium bromide (50 mg kg^{-1} i.v.).

pre-8-OH-DPAT response to cooling. The animal was then warmed. Nerve activity recovered to the pre-injection level 52 ± 12 min after the injection in four to six animals (data not shown). In the other two animals, nerve activity did not recover during the 1 h observation period. WAY-100635 (0.1 mg kg^{-1}) was administered approximately 20 min after readministration of 8-OH-DPAT (0.1 mg kg^{-1}) in three rabbits. In each case, WAY-100635 restored ear pinna sympathetic nerve discharge to the level recorded before 8-OH-DPAT (data not shown). Five min after administration of WAY-100635 the amplitude of the discharge was $159 \pm 65\%$ of the amplitude before 8-OH-DPAT ($n = 3$).

Administration of 8-OH-DPAT did not change ($P > 0.05$, $n = 4$) the latency, the amplitude or the duration of sympathetic nerve discharge elicited by single pulse stimulation of the cervical sympathetic trunk (Fig. 4A and B). Administration of hexamethonium abolished the evoked response (Fig. 4C and D).

DISCUSSION

Our experiments provide the first demonstration, in any species, that 5-HT_{1A} receptors have a powerful inhibitory effect on activity in the central neural pathway mediating temperature-related activation of sympathetic outflow to the cutaneous vascular bed. In conscious unrestrained rabbits, stimulating 5-HT_{1A} receptors with 8-OH-DPAT delayed constriction of the ear pinna vascular bed elicited by subsequently exposing the rabbit to a cold environment, and reversed cold-induced cutaneous vasoconstriction when administered after the cold exposure. The specific 5-HT_{1A} receptor antagonist WAY-100635 prevented and reversed the vasodilating action of 8-OH-DPAT, and prevented the fall in body temperature.

The dose of 8-OH-DPAT that entirely reversed cold-induced cutaneous vasoconstriction (0.1 mg kg^{-1}) is at the low end of the range of doses found to decrease body temperature in rats (Hjorth, 1985; Gudelsky *et al.* 1986; Cryan *et al.* 1999). Since the ear pinna is a major vascular bed for heat-exchange in the rabbit (Grant *et al.* 1932) and since body temperature fell, it is likely that loss of heat from the body via dilated cutaneous vessels contributes to the fall in body temperature occurring in association with 8-OH-DPAT. The smaller temperature fall in rabbits compared with rats may be related to the difference in body size. Since body temperature is a complex variable, depending on the relationship between heat production and heat loss, our findings explain why the hypothermic effect of 8-OH-DPAT might be greater in a colder environment (Nicholas & Seiden, 2003).

Our electrophysiological recordings from postganglionic sympathetic axons accompanying the ear pinna cutaneous

vessels confirm that nerve discharge is responsive to changes in skin and core body temperature in the rabbit (Riedel *et al.* 1972), in the manner also described for rat tail sympathetic nerve discharge (Owens *et al.* 2002). Activation of 5-HT_{1A} receptors with 8-OH-DPAT substantially reduced ongoing cutaneous sympathetic nerve activity, and substantially prevented the increase in cutaneous sympathetic nerve activity normally elicited by reducing the temperature of the water in the jacket surrounding the animal. In contrast, 8-OH-DPAT did not affect nerve discharge evoked by electrical stimulation of preganglionic sympathetic axons in the cervical sympathetic trunk. Thus the cutaneous sympathoinhibitory action of the drug is substantially within the central nervous system, in the brain and/or spinal cord, but not in the periphery.

5-HT_{1A} receptors occur in the CNS pathway regulating cold-induced cutaneous sympathetic vasomotor activity

Because 8-OH-DPAT inhibits a naturally induced normo-thermic response, it is likely that the neurons with 5-HT_{1A} receptors normally participate in the central neural regulation of this response. Our findings thus suggest the presence of inhibitory 5-HT_{1A} receptors in the central sympathetic pathway that normally regulates cutaneous vasoconstriction in response to exposure to a cold environment. However, although the 5-HT_{1A} antagonist WAY-100635 prevented and reversed the cutaneous vasodilating activity of 8-OH-DPAT, when administered at 26°C the antagonist did not change baseline ear pinna flow; nor did it alter physiologically elicited cutaneous vasoconstriction when administered before the rabbit was transferred to the 10°C environment, or prevent the physiological cutaneous vasodilatation normally elicited by transferring the rabbit from cold to warm. Thus, although 5-HT_{1A} receptors are linked in to the central pathway normally regulating the sympathetic vasoconstrictor response to cold, in the physiological situation they are not essential links in this pathway.

Understanding of the cellular physiology of 5-HT_{1A} receptors derives largely from studies of neurons in the dorsal and median raphe nuclei in the pons and midbrain (Sprouse & Aghajanian, 1987). These 5-HT_{1A} receptors are considered to be inhibitory somatodendritic autoreceptors present principally on neurons that synthesize 5-HT (De Vry *et al.* 1998; Barnes & Sharp, 1999). The electrophysiological studies that have focused on raphe magnus/pallidus neurons (Pan *et al.* 1993; Bayliss *et al.* 1997; Mason, 1997) support the autoreceptor view. However the assumption that 5-HT_{1A} receptors are exclusively or even principally present on 5-HT perikarya has recently been brought into question for the dorsal raphe nucleus (Kirby *et al.* 2003). The receptors seem also to be present on non-5-HT neurons in this nucleus.

Because a major subclass of 5-HT_{1A} receptors are thought to be autoreceptors and not to receive synaptic inputs, it has been difficult to determine how they are physiologically integrated into neural circuitry regulating physiological functions. The 5-HT_{1A} antagonist WAY-100635 potently and selectively antagonizes the actions of specific 5-HT_{1A} pharmacological agonists, but so far the antagonist, given by itself, has not been shown to have major effects on physiological processes. This is also consistent with the idea that the 5-HT_{1A} receptors relevant to our results are non-innervated somatodendritic receptors, not direct links in neural pathways mediating physiological processes.

Medullary raphe region and 5-HT_{1A} inhibition of cutaneous sympathetic vasomotor activity

Regulation of cutaneous blood flow is coordinated, at the lower brainstem level, by bulbo-spinal sympathetic premotor neurons located in the rostral midline medulla oblongata, in raphe magnus/pallidus and the parapyramidal region (Blessing & Nalivaiko, 2000; Nalivaiko & Blessing, 2001; Tanaka *et al.* 2002). In conscious rats, focal inhibition of neuronal activity in a similar raphe region causes a fall in body temperature (Zaretsky *et al.* 2003), presumably at least partially resulting from heat loss from the dilated cutaneous bed. 5-HT_{1A} receptors have been demonstrated to occur on raphe-spinal neurons present in the medulla oblongata (Helke *et al.* 1997). Our preliminary evidence indicates that local microinjection of 8-OH-DPAT into raphe magnus/pallidus in rabbits substantially inhibits resting postganglionic sympathetic nerve discharge (Y. Ootsuka and W. W. Blessing, unpublished observations). This is consistent with our hypothesis that a subpopulation of the cutaneous sympathoinhibitory 5-HT_{1A} receptors activated in our study is present on bulbo-spinal neurons in raphe magnus/pallidus and the parapyramidal region. Clearly there may be relevant 5-HT_{1A} receptors, either autoreceptors or post-synaptic receptors, in other regions of the nervous system.

Possible involvement of rostral medullary bulbo-spinal 5-HT neurons in the thermoregulatory process is suggested by the transneuronal tracing study of Smith and colleagues (1998), demonstrating that cutaneous sympathetic premotor neurons in this region include 5-HT-synthesizing neurons as well as non-5-HT-synthesizing cells. The lowest axonal conduction velocity for thermosensitive raphe-spinal neurons in the study by Rathner and colleagues (2001) was 3.4 m s⁻¹, suggesting that the particular neurons studied were not small 5-HT-synthesizing cells. However many of the 5-HT neurons, especially the subependymal cells, are small, with soma diameters in the order of 15 µm (Skagerberg & Bjorklund, 1985). Their descending axons are thus presumably thin and unmyelinated, making them difficult to activate in antidromic stimulation studies.

5-HT_{1A} receptors, anxiety, stress-induced hyperthermia and cutaneous blood flow

Body temperature can increase in anxiety-provoking situations (Zethof *et al.* 1995; Oka *et al.* 2001). 5-HT_{1A} receptor agonists reduce this stress-induced hyperthermia (Groenink *et al.* 1996; van der Heyden *et al.* 1997; Olivier *et al.* 1998; Mendoza *et al.* 1999; Pattij *et al.* 2002), and heat loss via cutaneous vasodilatation could contribute to this reduction. 5-HT_{1A} agonist drugs are in clinical use as anxiolytic agents (De Vry *et al.* 1998). Buspirone, an anxiolytic with marked 5-HT_{1A} agonist properties, causes a fall in body temperature both in experimental animals and in humans, and buspirone decreases stress-induced hyperthermia as well as the increase in skin conductance elicited by exposing humans to a sudden aversive white noise stimulus (Lecci *et al.* 1990; Young *et al.* 1993; Zethof *et al.* 1995; Bond *et al.* 2003). Our present study suggests that cutaneous vasodilatation as a result of 5-HT_{1A} receptor activation is likely to contribute to the hypothermic effect of buspirone-like anxiolytic agents.

Clozapine and olanzapine, atypical antipsychotic agents with anxiolytic properties, reverse cutaneous vasoconstriction and hyperthermia elicited by 3,4-methylenedioxymethamphetamine (MDMA, ecstasy), at least partially via increased heat loss secondary to the marked cutaneous sympathoinhibitory actions of these drugs (Pedersen & Blessing, 2001; Blessing *et al.* 2003). Clozapine's complex pharmacological profile includes 5-HT_{1A} agonist and 5-HT_{2A} antagonist properties (Mason & Reynolds, 1992; Arnt & Skarsfeldt, 1998; Barnes & Sharp, 1999). The present study demonstrates that 5-HT_{1A} agonist effects could contribute to cutaneous sympathoinhibition and vasodilatation induced by clozapine and olanzapine. A recent study suggests that 5-HT_{2A} antagonism could also contribute (Blessing & Seaman, 2003).

Conclusion

Our findings suggest that inhibitory 5-HT_{1A} receptors are present in the CNS pathway normally activating cutaneous sympathetic vasomotor nerve activity in response to cold. Neuronal localization of these receptors may include the perikarya and dendrites of bulbo-spinal premotor sympathoexcitatory neurons in the rostral medullary raphe region, including a population of neurons that also synthesize 5-HT.

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Serotonin syndrome from venlafaxine-tranylcypromine interaction.

Brubacher JR, Hoffman RS, Lurin MJ.

New York Poison Control Center, NY 10016, USA.

Excessive stimulation of serotonin 5HT1A receptors causes a syndrome of serotonin excess that consists of shivering, muscle rigidity, salivation, confusion, agitation and hyperthermia. The most common cause of this syndrome is an interaction between a monoamine oxidase inhibitor (MAOI) and a specific serotonin reuptake inhibitor. Venlafaxine is a new antidepressant agent that inhibits the reuptake of serotonin and norepinephrine. We report a venlafaxine-MAOI interaction that resulted in the serotonin syndrome in a 25 y-old male who was taking tranylcypromine for depression. He had been well until the morning of presentation when he took 1/2 tab of venlafaxine. Within h he became confused with jerking movements of his extremities, tremors and rigidity. He was brought directly to a hospital where he was found to be agitated and confused with shivering, myoclonic jerks, rigidity, salivation and diaphoresis. His pupils were 7 mm and sluggishly reactive to light. Vital signs were: blood pressure 120/67 mm Hg, heart rate 127/min, respiratory rate 28/min, and temperature 97 F. After 180 mg of diazepam i.v. he remained tremulous with muscle rigidity and clenched jaws. He was intubated for airway protection and because of hypoventilation, and was paralyzed to control muscle rigidity. His subsequent course was remarkable for non-immune thrombocytopenia which resolved. The patient's maximal temperature was 101.2 F and his CPK remained < 500 units/L with no other evidence of rhabdomyolysis. His mental status normalized and he was transferred to a psychiatry ward. This patient survived without sequelae due to the aggressive sedation and neuromuscular paralysis.

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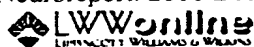
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**Temperature set-point changes induced by DA D2/3 and 5-HT1_A receptor agonists in the rat.****Oerther S.**

Department of Physiology and Pharmacology, Karolinska Institutet,
Stockholm, Sweden.

The DA D2/3 receptor agonist 7-OH-DPAT (2 micromol kg⁻¹) and the 5HT1A receptor agonist 8-OH-DPAT (0.6 micromol kg⁻¹) both produced a marked and similar decrease in core temperature of 3-4 degrees C at 10 and 2 degrees C ambient temperature. At 30 degrees C there were no, or weak, effects. The decrease in core temperature was accompanied by a sudden increase in tail temperature, followed by a decrease as core temperature returned to basal values. The results suggest that the hypothermia produced by the respective DA D2/3 and the 5-HT1A receptor agonists 7-OH-DPAT and 8-OH-DPAT is an active process, in all probability due to changes in a hypothalamic set-point for temperature regulation.

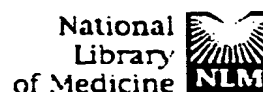
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The selective 5-HT(1A) receptor antagonist p-MPPI antagonizes sleep-waking and behavioural effects of 8-OH-DPAT in rats.

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Systemic administration of the selective 5-HT(1A) receptor agonist 8-hydroxy-2-(di-n-propylamino)tetralin HBr (8-OH-DPAT) increases waking and reduces slow wave sleep (SWS) and rapid eye movement (REM) sleep in the freely moving rat. The selective 5-HT(1A) antagonist 4-(2'-methoxy-phenyl)-1-[2'-(n-2"-pyridinyl)-p-iodobenzamido]-ethyl-piperazine (p-MPPI) induces a dose-related decrease in REM sleep. The present study examined p-MPPI's potential as an antagonist of the sleep and waking responses elicited by 8-OH-DPAT. Also, the experiments explored the ability of p-MPPI to block behavioural reactions of the 5-HT syndrome induced by 8-OH-DPAT, and whether p-MPPI induced any behavioural effects of its own. This study demonstrated that pre-treatment with p-MPPI (5 mg/kg intraperitoneal (i.p.)) 30 min before 8-OH-DPAT (0.375 mg/kg subcutaneously (s.c.)) reduced the effect of 8-OH-DPAT on waking and REM sleep. Also, p-MPPI (5 and 10 mg/kg i.p.) reduced the effect of 8-OH-DPAT on locomotion and partially or completely antagonized hindlimb abduction and flat body posture. No overt behavioural change was produced by p-MPPI alone. Thus, p-MPPI behaved as a true 5-HT(1A) antagonist.

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Changes in sleep and wakefulness following 5-HT_{1A} ligands given systemically and locally in different brain regions.

Bjorvatn B, Ursin R.

Department of Physiology, University of Bergen, Norway.

Serotonin (5-HT) has been implicated in the regulation of vigilance, but whether 5-HT is important for sleep or waking processes remains controversial. This review addresses the role of 5-HT_{1A} receptors in sleep and wakefulness. Systemic administration of 5-HT_{1A} agonists consistently increases wakefulness, whereas slow wave sleep (SWS) and REM (rapid-eye movement) sleep are reduced. However, systemic 5-HT_{1A} agonists also produce a delay increase in deep slow wave sleep, or an increase in slow wave activity. Intrathecal administration of a selective 5-HT_{1A} agonist produces an increase in SWS, whereas wakefulness is reduced, presumably by stimulating 5-HT_{1A} receptors located presynaptically on primary afferents in the spinal cord. Microinjection of serotonin into the region of the cholinergic basal ganglia neurons produces an increase in slow wave activity, presumably by stimulating 5-HT receptors. Microdialysis perfusion of a selective 5-HT_{1A} agonist into the dorsal Raphe nucleus causes an increase in REM sleep, whereas the other sleep/wake stages are unaltered. The REM sleep increase is likely due to a decrease in 5-HT neuronal activity, and thereby reduced 5-HT neurotransmission in projection areas, e.g. the laterodorsal and pedunculopontine tegmental nuclei. Direct injection of a selective 5-HT_{1A} agonist into the pedunculopontine tegmental nuclei reduces REM sleep, consistent with such a hypothesis. These complex sleep/wake data of 5-HT_{1A} ligands suggest that 5-HT_{1A} receptor activation may increase waking, increase slow wave sleep or increase REM sleep depending on where the 5-HT_{1A} receptors are located within the central nervous system.

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1: Psychopharmacology (Berl). 1994 Dec;116(4):433-6.

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Inhibition of REM sleep by ipsapirone, a 5HT1A agonist, in normal volunteers.**Gillin JC, Jernajczyk W, Valladares-Neto DC, Golshan S, Lardon M, Stahl SM.**

University of California, San Diego.

In order to test the hypothesis that serotonergic mechanisms inhibit REM sleep via a 5HT1A receptor, we administered placebo and ipsapirone (10 and 20 mg by mouth 15 min before bedtime) to ten normal volunteers in a double blind fashion. Ipsapirone is a relatively selective 5HT1A receptor agonist. As predicted, ipsapirone prolonged REM latency and Mean Latency to Eye Movements (M-LEM), a measure of time between onset of REM sleep and the first eye movement of the REM period, and REM% at both doses compared with placebo. It also reduced sleep efficiency and total REM sleep time at the highest dose. These results support the hypothesis that systemic stimulation of 5HT1A receptors prolong REM latency and inhibit REM sleep.

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